Neuropsychology of deep brain stimulation in neurology and psychiatry

Alexander I. Troster

Department of Neurology, University of North Carolina School of Medicine at Chapel Hill, 3114 Bioinformatics Building (CB 7025),Chapel Hill, NC 27599-7025, U.S.A

TABLE OF CONTENTS

1. ABSTRACT

Deep brain stimulation (DBS) experienced resurgence in the 1990s when limitations in pharmacotherapy and ablative surgery for movement disorders (including neuropsychological deficits) were appreciated. Subthalamic DBS for Parkinson's disease has received the most empirical attention and may entail cognitive and psychiatric adverse events in approximately 10% of patients. This article reviews the cognitive alterations after thalamic, pallidal, and subthalamic DBS for movement disorders (including, Parkinson's disease, essential tremor, and dystonia) and the possible etiology and mechanisms underlying neurobehavioral changes. Initial studies of neurobehavioral outcomes of DBS for emerging indications such as epilepsy, obsessive compulsive disorder, depression, Tourette's syndrome, and persistent vegetative or minimally conscious state are also reviewed. DBS for currently accepted indications appears safe from a cognitive standpoint in that the procedure is associated with typically transient, mild, and circumscribed cognitive alterations (most commonly in verbal fluency), and improved mood state and quality of life. A minority of patients experience more widespread, persistent, or serious cognitive and psychiatric sequelae, although research to date has failed to identify reliable risk factors for such adverse events.

2. INTRODUCTION

Electrical stimulation of the brain and observations of its effects on behavior in non-human animals for experimental purposes preceded the first use of electrical stimulation in humans by many years. The first experimental study of direct brain stimulation in a human (1) reported upon in 1874 was of muscle contractions and convulsions induced by contralateral brain stimulation in a woman being operated for abscesses in the brain. Though electrical stimulation was used clinically by Horsley for intraoperative localization in the 1880s,(2) the first report of the use of *chronically* implanted electrodes for experimental purposes was not published by Delgado until 1952,(3) and chronic electrical stimulation of brain structures for *therapeutic* purposes was not carried out until the middle of the 20th century, and then primarily for psychiatric conditions.(4, 5) Early brain stimulation also differed from that of today in that stimulation was often applied intermittently, electrodes were typically explanted again after weeks to months, and pulse generators or stimulators were external to the patient. In some instances the electrodes were used for recording neural activity and for stimulation specifically to avoid neurobehavioral complications from subsequent lesioning treatments for Parkinson's disease (PD).(6) In other cases, the electrodes were used for therapeutic stimulation. For example, in the

case of movement disorders, patients with Wilson's disease, dystonias, and PD had 24 to 40 electrodes (connected to 4 to 6 bundles of externalized wires) implanted into thalamus and striatopallidal nuclei, and later presented for 10-25 trials of stimulation once or twice per week via an external stimulator.(7) The first report of a fully implantable stimulator system used to chronically treat a movement disorder (tremor associated with multiple sclerosis) was published in 1980.(8)

Given concerns about the potential neurobehavioral morbidity associated with especially bilateral and ablative surgery for movement disorders,(9) it is important to address neurobehavioral functioning and quality of life outcomes of DBS.(10, 11) Similar evaluations of neurobehavioral and quality of life outcomes have been conducted for some time for resective epilepsy surgery, and detailed neuropsychological evaluations are likely to keep a central place in DBS for epilepsy. Similarly, meticulous, quantitative neurobehavioral and quality of life outcome documentation will be imperative if DBS is to find acceptance for psychiatric conditions given the controversy and ethical issues surrounding psychosurgery and functional neurosurgery.(12-15)

3. CONTENT AND PURPOSE OF NEUROPSYCHOLOGICAL EVALUATION FOR DBS

Typical neuropsychological evaluation entails a review of medical records, interviews with patient and family, observation of behavior, and administration and scoring of psychometric test instruments. Domains of functioning assessed in most evaluations include intelligence or overall level of cognitive functioning, attention and working memory, executive functions, language, visuoperceptual and spatial functions, motor function, memory, mood state, and quality of life. Evaluation may also be sought for personality, coping responses and stressors. It is the standardized, quantitative method of assessment of cognition, emotion, and behavior that sets neuropsychology apart from behavioral neurology and neuropsychiatry. The various sources of information are integrated to profile the patient's neurobehavioral strengths and weaknesses and to arrive at inferences about the suitability of DBS for that person from a neurobehavioral perspective. As noted by Okun and colleagues,(10) however, specific neurobehavioral criteria for inclusion/exclusion for DBS are lacking, and controversy surrounds what constitutes acceptable vs. unacceptable levels of cognitive impairment for entry into DBS. Though some general guidelines have recently been proposed in the pre-surgical evaluation of persons with PD,(16) given the current state of knowledge about the neuropsychological effects of DBS and risk factors for cognitive morbidity, prognostic statements are probably best phrased in terms of broad bands of probability.

The pre-operative neuropsychological evaluation also has several purposes other than facilitating decisions about surgical candidacy and include establishment of a baseline against which to evaluate potential post-operative

changes, and differential diagnosis. Other issues that can be addressed in neuropsychological evaluation are the capacity to consent to treatment, including the ability to perceive a choice to seek and refuse a given treatment, to choose among possible treatments, and the ability to appreciate the possible consequences of each of these courses of action. Evaluation of cognition, mood state and coping can facilitate decisions regarding a patient's ability to cooperate with the arduous pre-surgical evaluation process, operation and post-operative care, and patient and family expectations of surgical outcome, and the relationship of these expectations to potential satisfaction with outcomes can be examined.

Post-operative neuropsychological evaluation not only serves to document outcomes. In the event that complications emerge, such an evaluation facilitates decisions about whether cognitive, emotional and behavioral changes are related to surgical intervention or operative complications, deep brain stimulation (DBS), medications, disease progression, seizure activity, or emotional and psychosocial factors, thereby facilitating rehabilitation planning.

4. PARKINSON'S DISEASE

Three anatomical targets for DBS have been the subject of extensive investigation: thalamus (generally the *nucleus ventralis intermedius (Vim)), globus pallidus internus (GPi)*, and the *nucleus subthalamicus (STN)*. A handful of studies have recently explored DBS of the *nucleus tegmenti pedunculo-pontinus (PPN)* for PD (17) as well as DBS of zona incerta (18)and pallidofugal fibers.(18) Vim DBS is now rarely used for PD. Although STN is targeted more frequently than GPi given the possibility of greater medication reduction, stronger antiakinetic effects, and lesser stimulation energy requirement with STN DBS. An adequately powered randomized comparison of STN and GPi remains in progress.(19)

4.1. Thalamic stimulation

Three studies have reported detailed neuropsychological outcomes after thalamic DBS for PD, and none showed evidence of significant, wide-ranging cognitive changes.(20-22) Thalamic stimulation, unlike thalamotomy for PD, did not entail declines in verbal fluency or memory, though Loher *et al.* (22) did find, in a comparison of patients on and off stimulation, statistically significantly worse verbal memory in those having left thalamic DBS. In another comparison of cognition on and off stimulation, while on and off medication, Tröster and colleagues(23) found a post-operative decrement in verbal fluency in a single case, but stimulation per se, in both the medication on and off conditions, was associated with improved verbal fluency. In essence, surgery and stimulation had apparently opposite effects on fluency. Isolated, subtle improvements (possibly practice effects) have been observed on certain tasks: Caparros–Lefebvre *et al.* (20) observed better performance on a card sorting task days after surgery, while Tröster *et al.* (21) observed improved delayed recall of prose and recognition of a word

list, and somewhat better naming, about four months after surgery. In a 12-month follow-up of five of the patients reported upon by Tröster et al.,(21) Woods and colleagues (24) found that gains in verbal fluency and memory were maintained.

Few studies have examined mood states and health-related quality of life (QOL) after thalamic DBS. Caparros-Lefebvre et al.(20) found an improvement in mood state (depressive symptoms) 4-10 days after surgery. QOL improvements did not attain statistical significance in the study by Straits-Tröster et al.,(25) but this may reflect that a generic QOL measure, probably less sensitive to change than a disease-specific measure was used, and that the sample was small. Consistent with this hypothesis, QOL gains among five patients on a disease-specific instrument, the Parkinson Disease Questionnaire (PDQ), were still observed 12 months after unilateral thalamic DBS.(24)

4.2. Pallidal stimulation

Unilateral GPi DBS appears cognitively safe, although this conclusion is tempered by the limited number of small-sample studies published. Tröster and colleagues,(26) in nine patients undergoing unilateral pallidal DBS, found that none of the patients experienced significant changes in overall level of cognitive functioning three months after surgery. As a group, the patients demonstrated statistically significant declines in visuoconstructional ability and verbal fluency, but the changes were rarely of clinical significance. Subsequent studies yielded similar findings. Vingerhoets et al.,(27) found no statistically significant declines in cognitive functioning after unilateral GPi DBS and even when using a very liberal criterion of impairment (a test score falling 1 SD below the mean of normative samples), they noted that only six of the 20 patients showed *any* decrement (i.e., an increase, no matter how small, in the percentage of tests in the impaired range). These patients tended to be older and were taking higher medication dosages prior to surgery than patients showing no change or improvement. Merello et al.,(28) observed no significant changes on neuropsychological tests among six cases.

Safety of bilateral GPi DBS has been addressed in a handful of studies, and most found that the procedure is relatively safe from a cognitive standpoint. Ardouin et al.,(29) among 13 bilateral GPi DBS cases, found no significant changes in average test scores three months (Grenoble subjects, n=8) or six months (Paris subjects, n=5) after surgery. Pillon et al. (30) found no cognitive morbidity in a probably overlapping group of patients at 12-month follow-up, and the performance on experimental tasks of five GPi DBS patients at six months was no different on and off levodopa. Ghika et al.(31), too, found no significant changes in neuropsychological test scores three months after contemporaneous bilateral GPi DBS electrode implantation (n=6). Though these studies support the cognitive safety of GPi, some patients may develop cognitive morbidity. Only one case study with MRI-confirmed electrode location has reported significant executive dysfunction ensuing from bilateral GPi DBS.

(32) Importantly, when the stimulators were turned off, the impairment was partially reversed, thereby suggesting a direct role of stimulation in the neuropsychological deficit. Relatively isolated cognitive impairments were reported by the Toronto group.(33) Among four patients, there was a significant decrease in backward digit span. Verbal fluency was administered to only one patient, who demonstrated a decline on this task. The decline sometimes seen in verbal fluency after GPi DBS(26, 34) may be related to word search or executive strategy changes: patients seem to shift less efficiently between word categories when searching for words.(35)

To determine whether a second surgery (i.e., a staged bilateral procedure) carries cognitive risks relative to the first surgery, Fields et al. (36) examined neuropsychological functioning in six patients before surgery, two months after the first operation, and again three months after the second operation. No patient experienced significant declines in cognition and delayed recall was improved relative to baseline following the second operation. Rothlind and coworkers(37) recently reported on a randomized comparison of staged, bilateral GPi and STN DBS in 42 patients and also found that minimal cognitive changes ensued from the second relative to the first operation. Semantic verbal fluency (the ability to quickly name items belonging to a category such as fruits) declined after left DBS regardless of whether the left side was operated first or second. Though phonemic verbal fluency also declined only after left DBS, a significant effect of the second surgery was not demonstrated.

It remains unclear whether GPi DBS is safer than alternative procedures such as pallidotomy or subthalamic (STN) DBS. Studies by Merello et al. (28) and Fields et al. (38) found the cognitive safety of pallidal DBS and pallidotomy to be comparable. Although some suggest that bilateral GPi DBS may entail less cognitive morbidity than bilateral STN DBS,(39-41) the only randomized comparison of the cognitive effects of GPi and STN DBS has failed to reveal substantial differences between the two treatments.(37) A larger, randomized trial comparing the effects (including the neurobehavioral consequences) of simultaneous bilateral GPi and STN surgery is nearing completion.(19)

Quality of life has only rarely been evaluated after GPi DBS for PD. Vingerhoets et al.(42) administered a generic QOL measure (Sickness Impact Profile; SIP) to 20 patients before and three months after unilateral GPi DBS. Significant improvements were evident in the Physical, Psychosocial, and Total scores. Among the 12 subscales, improvements were observed for ambulation, body care and movement, communication, sleep and rest, and eating. Straits-Tröster et al.,(25) in their sample of nine unilateral GPi DBS patients, also observed significant improvements in the Physical and Total scales of the SIP, but did not analyze scores on subscales.

Studies using self-report measures of mood state (Beck Depression Inventory) did not find improvements in depressive symptomatology,(25, 27, 29, 31, 42) but Fields

et al.(36) noted that patients experienced a reduction in anxiety. Higginson and colleagues(43) observed improvements in the autonomic, neurophysiologic, and subjective symptoms of anxiety in patients having undergone either unilateral GPi ablative surgery or DBS. As others(44-46) have noted, the clinical significance of these group (mean) changes on symptom inventories is unclear, and future studies would do well to deal with caseness, i.e., report on the number of cases meeting diagnostic criteria for a certain condition such as depression before and after surgery. A single case study has detailed hypomania and manic episodes after unilateral or bilateral GPi DBS,(47) but this morbidity may relate to an interaction between stimulation and medication. Similarly, it is unclear whether hypersexuality reported in isolated cases(48, 49) reflects a possible dopamine dysregulation syndrome, medication-stimulation interactions, or a phenomenon that is part of hypomania.

4.3. Subthalamic stimulation

Neurobehavioral outcomes after bilateral STN DBS for PD have been published much more frequently than for any other form of DBS or condition. Nonetheless, controversy exists about the frequency, nature, and extent of cognitive changes and the factors underlying for such changes. The reported frequencies with which cognitive changes occur after STN DBS is quite variable and this probably reflects differences in ascertainment methods (informal review suggests that studies using formal neuropsychological evaluation are more likely to find changes than are studies using undefined methods or screening instruments), patient selection criteria, operative technique, and pre- and post-operative patient management strategies. A recent review(50) estimated that cognitive problems are observed in 41% of patients after STN DBS, but the extent and nature of such problems was not elaborated upon.

Examination of clinical studies suggests that profound or wide ranging changes in cognition are probably fairly rare. Rodriguez-Oroz and colleagues(40) who carefully defined severity of impairment, found that severe impairments (meaning incapacitating ones) occurred in 1% to 2% of cases. Moderate impairments (requiring treatment or having mild functional impact), and mild deficits (having no functional impact) were more common, occurring in about 20% of patients. This latter number is quite similar to that reported in another series,(51) but considerably higher than the approximately 4% incidence of cognitive impairment observed in a recently published, controlled multicenter trial (although it is not clear how this impairment was established or defined).(52)

The majority of studies employing formal neuropsychological evaluations have been uncontrolled and used fairly small samples, and several recent reviews have highlighted the many methodological limitations of these studies.(10, 44, 45, 53, 54) These studies, with few exceptions,(33, 55-59) have generally observed small and circumscribed cognitive changes, most often in verbal fluency (timed oral word generation according to different lexical and semantic constraints).(29, 30, 37, 57, 59-77).

Even among the studies reporting more widespread cognitive declines there is disagreement as to the clinical meaningfulness of cognitive changes -- in contrast to Saint-Cyr and colleagues(58), and Smeding and her colleagues,(59) Alegret and her coworkers (55) interpreted the observed cognitive changes *not* to be of clinical significance.

Less still is known at this time about the neurocognitive effects of unilateral or staged STN DBS. Morrison *et al.*(69) were the first investigators to publish neuropsychological findings pertaining to unilateral STN DBS. In their group of three patients, few cognitive changes were observed. Two of three patients (one left and one right DBS) showed improved category fluency, while two (one left, one right DBS) showed decrements in letter verbal fluency. Two patients (both left DBS) also showed poorer performance on the Stroop task and on an alternating fluency task. Although the sample is too small to reliably evaluate laterality effects of STN DBS, it appears cognitive changes can occur after both left and right STN DBS. A more recent randomized study of staged GPI and STN DBS afforded the opportunity to observe neuropsychological changes after unilateral surgery, and that study found verbal fluency declines after left DBS.(37) Although another study obtained neuropsychological data in only 12 of 24 patients, and did not examine the effects of laterality of surgery, that study also reported that unilateral STN DBS was associated with at least a trend toward decline in verbal fluency (while improvement in mental flexibility was attributed to possible practice effects).(78)

Because many of the neuropsychological studies of STN DBS have small sample sizes, it is prudent to emphasize and examine in greater detail the outcomes of controlled studies comparing neuropsychological changes in operated and unoperated PD groups. Unfortunately, there are only five such studies (excluding the handful of controlled studies limiting themselves to assessment of language or including only cognitive screening examinations) and each has significant methodological and/or conceptual limitations. The first published controlled neuropsychological study of STN DBS by Gironell and coworkers(65) compared the outcomes in 8 patients with bilateral STN DBS, 8 patients undergoing unilateral pallidotomy, and 8 unoperated PD patients. Surgical patients were tested on their medication 1 month before and 6 months after surgery, while the control group was retested after 6 months. In that study, a selective decline in semantic verbal fluency was observed in the STN DBS group.

Moretti and colleagues,(68) comparing the performance of nine patients, 1-, 6- and 12 months after surgery to a group of nine unoperated PD patients, found a decline at every time point relative to both baseline and control group performance in verbal fluency and in the Stroop task, on which performance was slower and more error-prone after surgery. A third controlled study made similar observations, although the methodology differed. The study by Morrison and colleagues(70) evaluated 17 patients (two of whom had had a prior pallidotomy) before and three to

four months after STN DBS, and 11 PD patients on medical therapy on two occasions, about 9 weeks apart. The impact of medical therapy in the STN DBS patients is difficult to evaluate because 5 of the 17 patients were tested off medication, while 12 were tested on medication. A desirable feature of the study is that a subset of the STN DBS patients (13) were tested twice after surgery, once with the stimulators turned on, and once with the devices turned off. The surgery effect (operationally defined as the difference between baseline and post-surgical "stimulation off" scores relative to the change in the control group's scores) was limited to mild decrements in language and attention. The procedure as a whole (the effect of surgery plus stimulation) was associated with subtle declines in delayed verbal recall and language. However, the effect of stimulation per (comparing test performance with stimulators turned on and off relative to change observed in the control group) revealed no significant changes. Similar to these earlier studies, the recent study by Cilia and others(79) also observed only circumscribed cognitive declines, specifically in semantic verbal fluency, 12 months after DBS in comparison to pre-surgical baseline and control group performance.

Another controlled study has found more widespread and serious cognitive changes. Smeding and associates(59) evaluated 99 STN DBS patients, on medication, within 3 months before surgery and 6 months after surgery. The change in neuropsychological test scores was compared to the change observed among 36 medically treated PD patients tested twice, six months apart. Relative to the control group, the STN DBS group was reported to have more marked decline in overall level of cognitive function (approaching statistical significance), verbal fluency, delayed recall, and visual attention. Although quality of life was apparently improved and depression scores improved, the STN DBS group also showed diminished positive affect and increased emotional lability after surgery. Although this study is probably among the best (if not the best) available given the use of a control group and a fairly large sample, several important limitations, including several discussed by the study's authors, should be borne in mind when considering the potential significance of the reported findings. The study was not randomized. In addition, no comparison was made of neuropsychological functioning on and off stimulation so that it is not possible to determine whether stimulation per se exerted a negative effect on cognition, and accuracy of electrode placement is unknown. Even though some of the comparisons are statistically significant, the effect sizes associated with them are small to moderate. Perhaps a more critical issue is the statistical treatment of the data. The study's authors argue that a liberal statistical approach (using nonparametric statistics, not correcting for chance findings associated with a multitude of statistical comparisons, and the use of one-tailed significance tests) is appropriate since safety of the procedure is a primary consideration and one would presumably rather err by incorrectly concluding that a difference exists (Type I error) than to miss a true difference (Type II error). This position has merit, but some might question whether a slightly more conservative approach might still be adequately liberal. In particular, given that there usually is some heterogeneity among patients' test score changes (some show improvements, some declines, some no change on any given test), one might wonder whether the employed one-tailed significance testing approach is justifiable. Such an approach assumes a priori that a uni-directional change (presumably a decline) will occur, an assumption not supported by others' findings that reveal variability among individuals' outcomes and the observation that some test scores improve in groups of patients.(29, 62) Unfortunately, the frequency of sizeable negative and positive changes was not reported. Also, as noted by the authors of the study, some effects may have been medication-related: for example, the decline in memory was no longer significant from the change in the control group once anticholinergic medication intake was accounted for.

A major issue in interpreting the somewhat discordant neuropsychological findings of STN DBS studies is that many studies have relatively small sample sizes. The problem that attends such small samples is that studies may lack the power to detect effects. Woods and colleagues(54) found that only two of 30 studies reviewed had adequate power (above 0.8.0, where maximal power is 1 and minimal power is 0) to detect large cognitive effects. More alarmingly, none had sufficient power to detect cognitive changes associated with conventionally medium (or smaller) effect sizes. Given this limited power, and the general absence of effect sizes in statistical analyses, our laboratory recently undertook a quantitative meta-analysis of findings to date.(80) That study was based on a literature search of peer-reviewed, English-language studies from 1990 to April 2006 that reported interval or ratio data, provided pre- and post-operative data on at least one standardized neuropsychological test, and provided sufficient information to allow calculation of effect sizes. Given the large number of different test used in the literature, tests were assigned to the functional domains they are commonly accepted to primarily measure (e.g., verbal memory, language, attention). Of 40 studies identified, 28 met inclusion criteria, and this yielded a maximum combined sample size of 612 for calculation of the effect size of changes in the various domains of cognition. Analyses revealed that STN DBS (considered as a whole treatment procedure) was associated with moderate declines in verbal fluency and mild declines in verbal memory and executive function. Mild improvements were observed in psychomotor/information processing speed. Overall then, the uncontrolled, controlled, and meta-analytic findings are in general accord that STN DBS is relatively safe from a cognitive perspective. One must bear in mind, however, that metaanalysis does not, despite attaching greater weight to studies with larger samples, redress methodological shortcomings of the studies included in the analyses.

Given the declines in verbal fluency, memory, and executive function that might attend STN DBS (even if of small to moderate effect size), an issue becomes whether the factors underlying these changes can be isolated. The identification of potential risk factors for cognitive decline,

regardless of whether due to surgical intervention or DBS per se, has obviously important implications for facilitating the avoidance of cognitive morbidity. Unfortunately, attempts in this regard have not been very fruitful and studies have not reliably identified factors that underlie cognitive changes after STN DBS. One possibility is that suboptimal electrode placement or spread to non-motor (that is, limbic and associative) circuits(81-83) accounts for these cognitive and behavioral changes. Electrode placement, stimulator programming, and current spread issues might not be unexpected given the close proximity of motor, associative, and limbic territories within the structures targeted in DBS.(84)While there is no doubt that mis- or displaced electrodes can lead to serious neurobehavioral consequences that are at least partially reversible by revision of lead location or contact selection,(85) this does not imply that all neurobehavioral complications are related to electrode misplacement or suboptimal electrode contact selection. To date, a relationship has not been found between cognitive change and active electrode coordinates.(86) Similarly, assuming that less accurate electrode placement is associated with poorer motor outcome and that patients with poorer motor outcome would thus be more probable to have cognitive changes, a relationship has not been found between motor improvement (a proxy measure of electrode placement accuracy) and cognitive outcome.(59, 86) Of course, this lack of relationship might be an artifact in that there is among experienced treatment centers little range (and variability) in electrode location making it difficult to obtain a significant correlation between location and cognitive outcome. One might also argue that suboptimal electrode placement can be compensated for by adjusting stimulation parameters, such that even patients with cognitive and behavioral changes and poorly placed electrodes still have good motor outcomes. This proposal is supported by a recent study of two cases with PD in whom hypomania, yet good motor symptom control, could be reliably reproduced by stimulation via a contact located in the anteromedial portion of the STN.(87)

Attempts to reveal a relationship between stimulation parameters and cognitive outcome have also met with limited success, probably in large part because four stimulation parameters (polarity, frequency, amplitude, pulse width) can be varied, thereby yielding an almost infinite set of possible combinations of parameter adjustments. Not surprisingly then, the relationships of stimulation parameters to neuropsychological outcome have been explored retrospectively within narrow ranges of motorically beneficial or therapeutic stimulation settings. Another issue complicating identification of stimulation parameter relationships with cognitive outcome is that while various motor signs have known different time-response curves,(88) the timecourse of various cognitive responses to DBS is not known. Thus, it is not known how soon after turning stimulation on or off changes in cognition become apparent or dissipate. A report that various aspects of stimulation (such as higher frequency) are related to cognitive change(89) is tempered by the observation that parameters other than the one being evaluated were not held constant, making it difficult to identify clearly which parameters influence cognition and how they do so.

Another strategy to isolate an effect of stimulation on cognition is to compare test performance with stimulators turned on and off. In general, such comparisons have yielded few replicable effects,(30, 66, 70, 71, 74, 90-92) and even when statistically significant, such effects' clinical significance remains a matter of speculation. Only one study has examined different STN stimulation frequencies' effects on cognition, and that study reported differential effects of low frequency, high frequency, and no stimulation on verbal fluency.(93) Specifically, low frequency stimulation facilitated verbal fluency whereas high frequency stimulation disrupted word generation. A potential future avenue for exploring the effects of STN stimulation on cognition is to do so intra-operatively, though our experience shows that testing of awake, elderly patients withdrawn from medication is quite challenging and needs to be very brief.

Other studies examining potential correlates of cognitive change after STN DBS have failed to disclose relationships between cognitive change and depression(86) or dopaminomimetic medication changes.(59, 80, 86) Although a relationship between cognitive impairment and apathy may emerge 6 months to years after STN DBS,(64, 75) such a relationship was not evident three months after surgery.(75) Other potential risk factors for cognitive deterioration have not been confidently established, but include more advanced age (greater than 69 years)(33, 58, 69) and pre-existing cognitive deficits.(94-96) While age appears to predispose to post-operative confusional episodes(97), poorer executive function outcome in the long term after STN DBS,(64) it does not necessarily confer risk for poorer cognitive short-term outcomes.(37, 98) It is also important to note that although older persons and persons with poorer baseline executive functioning are more likely to develop dementia after STN DBS, the incidence of dementia after DBS may be no greater than that observed in medically treated patients.(99)

Because verbal fluency declines represent the commonest cognitive morbidity after STN DBS, several studies have attempted to identify the neural and cognitive mechanisms underlying these changes. That verbal fluency can be directly impacted by STN stimulation (rather than the treatment procedure as a whole) was elegantly shown in a study utilizing randomized, double blinded, high frequency (130 Hz), low frequency (10 Hz), and sham stimulation (presumably bilateral). Low frequency stimulation improved performance on four 1-minute verbal fluency tasks, whereas high frequency stimulation tended to produce a diminution. Regardless of the debate about whether electrodes properly placed in sensorimotor (dorsal) STN or misplaced electrodes account for cognitive changes, two potential mechanistic explanations for verbal fluency declines are probably the most credible: motor speech and cognitive. Were one to speculate that motor speech mechanisms underlie verbal fluency decrements, it would be sufficient to posit an effect of STN DBS on cortical-basal ganglionic motor circuits. In contrast, were

one to propose cognitive, and more specifically semantic or executive mechanisms as fundamental to DBS-induced verbal fluency changes, it would be necessary to speculate that: a) stimulation spreads beyond the motor circuit, b) that active electrode contacts are placed outside the putative motor area, c) that different stimulation patterns differentially affect various basal ganglia structures and downstream cortical regions,(100, 101) or d) that basal ganglia circuits are more open and inter-connected than held by accepted models (see Joel & Weiner).(102)

A motor speech explanation of verbal fluency declines after STN DBS appears at first blush paradoxical given motor improvements with DBS. However, one might argue that the range of effective stimulation for limb and speech motor programs is different.(103) The majority of studies find an improvement or no change in dysarthria after STN DBS(103-107) and these improvements are related to normalization of cerebral metabolic patterns associated with speech activation,(103) a finding paralleling that of normalization of cortical metabolism in good motor responders but not non-responders to DBS. When negative effects on motor speech do occur,(108) they may be related to misplacement of electrodes or stimulation at suboptimal parameters, dyskinesias related to medication and stimulation interactions,(106, 109) or an imbalance between right and left stimulation.(107) Indeed, Törnqvist *et al.*(110) have shown that using typical stimulation settings there was no difference on and off stimulation in speech intelligibility, but that intelligibility declined with higher stimulation frequencies and amplitudes.

Empirical evidence, albeit indirect, probably favors a non-motor speech explanation for verbal fluency changes. Support for a cognitive rather than motor mechanism underlying verbal fluency changes comes from a study with seven patients undergoing positron emission tomography (PET) while carrying out verbal fluency tasks with and without STN stimulation. Whereas motor function improved with stimulation, verbal fluency performance declined by 15 percent. In addition, verbal fluency differences between on and off stimulation were correlated with regional cerebral blood flow activation (verbal fluency - counting) decrements during on vs. off stimulation in the left inferior frontal and temporal gyri. A subsequent study has also noted verbal fluency declines to be related to regional cerebral blood flow decrements in dorsolateral prefrontal cortex, anterior cingulated, and the ventral caudate.(79) Other evidence supportive of cognitive and linguistic mechanisms underlying verbal fluency decrements after DBS are the findings that: (a) STN DBS affects semantic processing,(73) (b) motor speech decrements would affect performance on a range of expressive language tasks, yet verbal fluency decrements may be specific in that they can be accompanied by improvements on other expressive language tasks, including visual confrontation naming,(111) and (c) reductions in verbal fluency after pallidal surgery are associated with diminution of patients' efficiency in switching between lexical-semantic categories during word search and retrieval, thus implicating specific cognitive mechanisms in verbal fluency deterioration.(35, 112)

Consistent with the latter findings, STN DBS has been reported to be associated with diminished switching between categories, whereas clustering remains unchanged.(113)

Recent meta-analysis of 22 studies carried out between 1993 and 2004(114) yielded estimates that about 7% of patients develop depression after STN DBS, that hypomania or a manic episode occurs in about 2%, and that other psychiatric disorders such as hypersexuality, lability, psychosis, and hallucinations occur in 4% of patients. Similar figures were reported in a review by Temel and colleagues:(50) depression 8%, hypomania or mania 4%, anxiety disorders <2%, personality changes, hypersexuality, apathy, and aggressiveness <0.5.%, and coincide with the overall rate of psychiatric issues requiring treatment in 9% reported in a controlled study of 99 patients.(59) However, the range of the incidence of various behavioral alterations reported by different studies may be quite broad:(45) depression 1.5.% to 25%, attempted and completed suicide 0.5.% to 2.9.%, and (hypo)mania 4% to 15%. Another recent retrospective analysis reported transient mood disturbance in as many as 64% of patients.(115) Factors underlying this heterogeneity of outcomes may relate to patient selection/exclusion criteria, especially with regard to psychiatric illness, ascertainment and definition methods, surgical and post-operative management differences, and rigor of study methodology. In addition, the surgical experience of a center may play a significant role, in that morbidity typically decreases as center experience increases.(116) Our own informal review of studies raises the hypothesis that historically earlier published studies, studies with small samples (both of these factors may be associated with a treatment centers' experience), and studies with longer follow-up are apt to report a higher incidence of post-operative psychiatric morbidity. For example, one study of 11 patients over 5 years reported mania/hypersexuality in almost 20% and apathy in almost 10%.(61) Another study of 37 cases collected between 1996 and 1999, using 5-year follow-up, reported attempted suicide or suicide in 13.5.%, apathy in 22%, disinhibition in 35%, psychosis and/or hallucinations in 27%, aggression in 8%, and dopamine dysregulation syndrome (levodopa addiction) in 8%. In contrast, a recent, controlled study of 78 patients using a 6-month follow-up reported depression in 5%, suicide in 1%, and psychosis in 5%.(52) It is premature, however, to draw conclusions about the mechanisms of such behavioral changes and about the similarities and differences in long term outcomes between those patients having had DBS and those subjected to other treatments. Certainly, given the progressive nature of PD, one expects behavioral changes to emerge more frequently with longer disease duration. Potential mechanisms underlying psychiatric phenomena after DBS include a pre-operative vulnerability,(117) stimulation, effects of surgery, psychosocial stressors and adaptation, and alterations in medication after surgery. Stimulation in or in the region of the STN has been observed to lead to visual hallucinations,(118) pseudobulbar crying,(119) laughter and euphoria (120, 121) and depression. (122, 123) Acute mood changes tend to be provoked by stimulation dorsal or ventral to the target for

optimal motor control,(124) whereas apathy is associated with ventral and medial STN DBS,(75), hypomania with anteromedial STN DBS,(87) and delusions perhaps with medial stimulation.(125) Aggression occurs with stimulation in the region of the triangle of Sano,(126) though aggression has also been observed with presumably accurately placed STN electrodes.(127)

Of note also is the apparent disconnect between studies reporting post-operative depression and those using symptom rating scales and self-report inventories showing improvements in average scores of symptom severity. Several studies have reported improvement in depressive symptomatology (29, 41, 58, 128) when considering self-report mood state questionnaires. Similarly, studies disagree whether apathy does or does not increase after STN DBS.(75, 129) On one hand, studies reporting post-operative incidence of behavioral changes typically do not report change in caseness from pre-operative state, leaving it possible that incidence of psychiatric conditions actually improves from pre-operative levels. Indeed, a study has shown that the incidence of psychiatric illness may be greater among PD surgical candidates (before surgery) than among the PD population in general.(130) Alternatively, patients completing inventories or responding to questions on rating scales may underestimate or be relatively unaware of behavioral changes as might be indicated by discrepancies in the report of patients and their carepartners.(58)

Another topic of increasing interest has been the phenomenon of pathological gambling, and isolated cases of this condition have been reported after DBS.(59, 131) A large, retrospective study(132) identified 7 persons who had displayed with pathological gambling prior to surgery among 598 patients who underwent STN DBS. All patients' gambling improved after surgery, resolving on average 18 months after surgery, but 2 patients' condition worsened transiently. The improvement in gambling and other symptoms of dopamine dysregulation syndrome (e.g., off period dysphoria, non-motor fluctuations) paralleled the course of dopaminergic medication reduction after electrode implantation.

Several studies have convincingly shown that QOL improves after STN DBS.(133) Not only does QOL improve after DBS, but it improves more than with medical treatment as revealed by a controlled study.(52) In addition to improving patients' QOL, STN DBS also translates into gains in QOL of carepartners for at least two years.(134) However, not all domains of QOL improve comparably, and gains may be limited to physical aspects of QOL such as bodily discomfort, activities of daily living, mobility, and perceived stigma,(135, 136) though several studies also find improvement in other domains such as satisfaction with social, psychological and emotional functioning, one to three years after surgery.(137, 138) Recent studies found that QOL improvements may not be attained in patients older than 65 years patients (139) and that there is a negative relationship between advancing age and quality of life gains after DBS.(98) There appear to be no other robust presurgical predictors of QOL improvement,(137)

but improvement in bradykinesia appears to be one of the strongest correlates of QOL improvement.(137, 140) How much of the effect of motor improvement on QOL is direct is still unclear, and some of the benefit may be indirect via improvement in depressive symptomatology.(141) Whether the most common cognitive morbidity after STN DBS (i.e., verbal fluency decline) has a significant impact on QOL is unknown. Two studies have found significantly decreased satisfaction with communication,(63, 135) but the factors responsible for those specific QOL declines were not identified.

Few studies have attended to social adaptation after surgery, a complex issue that has been more adequately addressed in the epilepsy surgery literature. Recent studies consistently provide evidence that gains in motor function and QOL do not necessarily translate into improved social integration and adaptation.(142, 143) Familial relationships can be compromised after DBS,(143, 144) presumably especially when expectations of outcomes and perceived levels of functioning diverge between patient and carepartner. In addition, despite improvements in motor function and QOL, patients may not return to work – in one study, only 9/16 who were working before surgery had returned to work by 18-24 months after surgery.(143) Predictors of, and barriers to social adjustment remain to be identified.

5. ESSENTIAL TREMOR

Several studies have demonstrated the effectiveness of thalamic DBS in the reduction of postural and action tremor in patients with essential tremor (ET) with some studies showing that improvements persist to 6 years.(145-148) Limited case studies suggest that DBS of the white matter near the STN may also be effective for ET.(149-151) Neurobehavioral outcomes of DBS for ET are sparsely documented. One study(152) mentioned in passing that one of four ET patients experienced transient slowing of information processing. Detailed neuropsychological data pertaining to unilateral thalamic DBS in ET were presented by Tröster and colleagues (153) who found that among 40 patients with ET the only decrement observed involved lexical verbal fluency (in contrast to the absence of such an effect in PD). Improvements, possibly representing test-retest or practice effects, were observed in visuoconstructional skill and visuoperceptual gestalt formation, backward visual span, delayed prose recall and word list recognition (also seen in PD after thalamic DBS). In a follow-up study at 12 months following surgery, largely similar results were reported.(154) Improvements in delayed verbal memory, visual construction, visual perception, and dominant hand manual dexterity were maintained relative to baseline and patients demonstrated an additional improvement from baseline on a measure of verbal learning, perhaps reflecting a practice effect. Significant increases in performance were found between the 3- and 12-month evaluations on measures of verbal learning and concept formation. Twelve months following surgery, no significant declines were noted on any of the measures in comparison to baseline. However, four patients with baseline deficits in verbal

fluency showed substantial further decrements following surgery, suggesting that persons with poor verbal fluency prior to surgery may be more susceptible to exacerbation of this deficit by DBS.

Few studies have compared neuropsychological test performance with and without stimulation. One case report found that thalamic DBS may improve verbal fluency.(155) No differences were noted in other measures of attention, verbal memory, or visual perception. However, another study comparing performance on and off stimulation found that thalamic DBS may disrupt recall of a word list.(22) Because only two of the nine patients in this study had ET it is difficult to discern whether similar findings would be obtained in a larger sample of ET patients.

Little research has examined how well surgical and stimulation parameters might predict cognitive or ADL changes after DBS in ET. One study compared the characteristics of 27 ET patients with mild cognitive declines following surgery with those of 22 patients without such declines.(156) There were no significant differences between the two groups in baseline neuropsychological performance, disease duration and onset, demographics, or postoperative motor functioning, but a larger proportion of patients with cognitive declines had undergone left rather than right thalamic DBS. A significantly higher pulse width (PW) was used in the group with cognitive declines in comparison to the stable group and there was a significant association between cognitive decline and pulse width greater than 119 microseconds. It should be noted that all stimulation parameters' relationship to verbal fluency could not be evaluated simultaneously, and thus, the unique role of pulse width in verbal fluency declines remains unknown. Onset of ET after age 37 was another significant predictor of a worse cognitive outcome.

Several studies demonstrate effective reduction of disability and significant improvements in activities of daily living (ADL) such as writing and pouring, following DBS for ET.(157) Clinicians and patients have rated similar levels of improvement, ranging from 40% to 60%, on measures of ADLs such as the TADLS.(158, 159) Improvements of ADLs have been noted in comparisons of baseline and post surgical scores, in comparisons of stimulation turned on and off,(158, 160) and these improvements occur after both unilateral and bilateral DBS.(146) Such ADL improvements are associated with gains in QOL. Tröster and colleagues(153) found a reduction in anxiety symptoms three months after unilateral thalamic DBS surgery for ET. On the SIP (a generic QOL measure), improvements were found in Total and Psychosocial scores, and on the modified PDQ (a disease-specific measure), patients expressed significantly increased satisfaction with ADLs, communication, emotional functioning, and stigma. At 12-month follow-up, gains were maintained on the SIP Psychosocial scale and the modified PDQ Stigma, Activities of daily Living and Emotional Well-being scales.(154)

6. DYSTONIA

Primary or idiopathic dystonias vary in the body parts they affect but all involve involuntary muscle contractions that lead to abnormal posture, twisting, and repetitive movements. The earliest attempts to treat torticollis and dystonia with stimulation targeted the thalamus.(161, 162) The more recent case reports' findings that bilateral pallidal stimulation alleviates dystonia have been confirmed in larger series using blinded evaluation(163) and sham stimulation control,(164) but relatively few studies have evaluated neuropsychological functioning, mood and behavioral changes, and quality of life.

In an early case series, Morrison *et al.*(69) reported minimal cognitive change in two patients with dystonia who underwent right GPi DBS. One patient experienced a decline in verbal fluency, but both patients experienced improvements on some tests of attention and memory. In the most detailed neuropsychological study to date evaluating overall level of cognition, attention, executive functions, verbal fluency and verbal learning, mood state and QOL in 15 patients, Hälbig *et al.*(165) reported improvement in motor function following bilateral GPI DBS ranging from 26% to 93%. As compared to baseline there was no deterioration in patients' cognitive scores three to twelve months (mean = 6.5. months) following surgery as a group, although there was some variability in outcome such that some patients showed declines or improvements on one or more tests. Slight overall improvements were noted in part A of the Trailmaking test, a test of psychomotor speed and visual attention. There were no marked changes on measures of depression, anxiety, psychosis and mania. Overall QOL, measured with the PDQ designed for PD, improved 37% after DBS. Vidailhet and colleagues' study (163) of twenty-two patients using a blinded evaluation protocol revealed mean dystonia severity scores improved by an average of 51% twelve months after surgery. These authors found that, compared to pretreatment baseline testing, none of the patients experienced statistically significant declines in cognitive functioning as revealed by a cognitive screening instrument (MMSE) which may not be sensitive to the circumscribed cognitive dysfunction sometimes observed in dystonia. Pillon *et al.*(166) conducted a more comprehensive neuropsychological evaluation (of abstract reasoning, verbal intelligence, attention, executive function, verbal fluency, and verbal learning memory, and depressive symptomatology) in this same patient group, and also observed no negative impacts on cognition at the one-year study endpoint. Pillon and colleagues further noted that, as a group, patients showed mild but statistically significant improvements relative to baseline on measures of concept formation and reasoning, executive function, and memory. Whether these gains exceed expected practice or familiarity effects is unclear. QOL evaluated with the Medical Outcomes Study (MOS) 36-item Short-Form General Health Survey (SF-36) revealed significant improvements in only two of the eight domains evaluated (General health and Physical Functioning).(163)

STN DBS has also been successfully attempted in dystonia, and a recent study of four patients with primary, predominantly cervical dystonia found no "definitive" neuropsychological impairment across patients.(167) Examination of data, however, suggests the possibility of declines in language and visual memory in two of the four patients.

7. EPILEPSY

Ablative surgery for refractory epilepsy has been carried for a long time. Numerous neuroanatomical structures were also targeted to treat epilepsy with stimulation,(168, 169) with the earliest work targeting the anterior thalamus and cerebellum.(161, 170, 171) The relative absence of empirically documented neuropsychological outcomes after stimulation for epilepsy is surprising given the regularity of neuropsychological evaluation in ablative epilepsy surgery. Hodaie and colleagues(172) reported on anterior thalamic DBS in five patients with generalized tonic-clonic or secondarily generalized seizures. Although it was reported that family witnessed no behavioral changes, and that three patients' families reported improved cognition and activities of daily living, no supportive objective data were provided. Similarly, a pilot study of 14 patients(173) did not provide detailed neuropsychological data, but it was noted that two patients experienced depression and another two experienced increased irritability.

A placebo-controlled pilot study of centromedian nucleus stimulation in seven patients with either tonic-clonic, tonic, or complex partial seizures utilized tests of intelligence, speech and language, visual and verbal memory, visuospatial functions, attention, executive functions, and motor speed.(174) Detailed neuropsychological findings were not presented, but it was reported that no differences were observed between baseline scores and scores obtained on and off stimulation after surgery.

Hippocampal stimulation has been used in patients deemed at excessive risk of cognitive (memory) deficit after potential temporal lobe resection. One study reported neuropsychological evaluation resulted in four patients with complex partial seizures with or without secondary generalization who underwent left hippocampal DBS.(175) Patients underwent a three month baseline evaluation period and were again evaluated after DBS after three months on- and three months off stimulation. Though detailed data were not presented except for one patient, it was reported that no changes were observed in neuropsychological function when comparing test performance on and off stimulation and to baseline. A recent study failed to observe any significant cognitive changes after mammillothalamic DBS in three patients, though detailed data were, again, not provided.(176)

8. MULTIPLE SCLEROSIS

DBS does not represent a comprehensive treatment for multiple sclerosis (MS), but, like other surgical interventions used in this condition,(177) has application in the amelioration of specific symptoms, in this case tremor. The target used is generally the thalamic ventral intermediate (Vim nucleus), though the ventralis oralis posterior and anterior (VOP and VOA) nuclei have been stimulated in conjunction with Vim.(178) Recently it has been proposed that stimulation of the subthalamic region may be more effective than thalamic stimulation in controlling tremor associated with ET and MS,(179) and that tremor in MS may respond better to simultaneous stimulation of multiple rather than single targets, though not all studies find such an additive effect.(178, 180) A review of studies published from 1980 to 2002 makes clear that detailed neuropsychological outcome data remain unavailable.(181)

9. DEPRESSION

Functional neuroimaging findings implicate the subgenual cingulate in negative mood states and antidepressant treatment effects. On the basis of this observation Mayberg and colleagues(182) undertook DBS of the white matter tract adjacent to the subgenual cingulate gyrus in six patients with major depression (MDD) refractory to other therapies. Four of the six patients were deemed to respond to the treatment (50% reduction of symptoms at 6 months) and the patients did not experience significant declines in cognitive functioning as a result of the surgery. While a detailed discussion of neuropsychological test results has not yet been published, Mayberg and colleagues reported that when compared to pretreatment baseline evaluation, intelligence, language, and basic visual-spatial functioning remained stable after three and six months of stimulation. Moreover, improvements were noted in visuo-motor function, and on tests said to be sensitive to dorsolateral frontal function (verbal fluency), ventral prefrontal function, and orbital frontal function. Greenberg *et al.* (2005),(183) in a three-month study of five MDD patients undergoing bilateral DBS in the ventral portion of the anterior limb of the internal capsule and the adjacent dorsal ventral striatum ("VC/VS"), found that three patients experienced more than a 50% improvement in depressive symptoms while two other patients showed 24% and 17% improvements, respectively. Detailed neuropsychological data were not reported. Similarly, single case studies of thalamic peduncle DBS for depression,(184) and of GPi stimulation for dyskinesia in a depressed patient associated with amelioration of depression, did not report cognitive outcomes.

10. OBSESSIVE-COMPULSIVE DISORDER

Different structures have been targeted in DBS for treatment-refractory obsessive-compulsive disorder (OCD), including the anterior limb of the interior capsule, the nucleus accumbens and its environs, and the caudate, but all studies are based on only a few patients.(185) Only a handful of studies discuss the effect of bilateral DBS in the anterior limb of the internal capsule on cognition. Greenberg *et al.*(186) monitored treatment progress in eight of the original ten OCD patients in their study, and found

that chronic stimulation over a three-year interval induced a 25% or greater overall reduction in OCD symptom severity in six of the patients. Neuropsychological test results obtained after a mean of approximately ten months after surgery revealed that, as a group, these patients experienced no significant declines in cognitive performance relative to baseline testing, and no individual patient demonstrated a clear or pervasive pattern of decline. Significant overall improvements in passage recall, even when correcting for practice effects, were reported.

Gabriëls and co-workers(187) found that two of three patients they studied also experienced a significant reduction in OCD symptom severity subsequent to DBS surgery. Neuropsychological assessments, focusing especially on executive functions and attention, were performed prior to and one year after treatment. No significant deterioration in cognitive abilities was observed with DBS, but one patient tended to make more errors on a card sorting task (demanding of conceptualization and cognitive flexibility) after one year, and visual memory (for a complex figure) tended to improve.

More variable neuropsychological outcomes were reported in another study of four patients undergoing DBS of the anterior limb of the internal capsule for refractory OCD.(188) In those patients, who underwent DBS in a randomized "on-off" stimulation sequence of four 3-week blocks, evaluation of attention, working memory, processing speed, verbal fluency, and cognitive flexibility revealed no consistent pattern of changes across subjects comparing the baseline and four post-surgical evaluations. A more extensive test battery done at baseline and after 6 months of continuous stimulation also revealed no consistent neuropsychological alterations. However, isolated patients showed improvements and declines in executive function tests.

Aouizerate and colleagues,(189) in a case report, found that an OCD patient undergoing DBS in the ventral caudate experienced a clinically significant reduction in symptom severity after one year of stimulation at 130 Hz. A comparison of pretreatment cognitive test scores to those obtained at one and six month intervals following chronic stimulation showed no impairment of cognition, and revealed improvements in attentional and executive functions as well as in visual and verbal memory. Of note, Pool(5) had used chronic caudate stimulation in a depressed patient already in 1948, though cognitive outcome was not reported. A report of right nucleus accumbens stimulation did not provide neuropsychological data.(190) One case study of intraoperative stimulation during electrode placement for OCD in the anterior limb of the internal capsule in the vicinity of the nucleus accumbens showed that fear and panic could be induced with stimulation and reliably replicated by turning the stimulation on or off.(191) This finding parallels the observation of anxiety symptoms elicited by intraoperative rostral cingulate stimulation in the course of ablative surgery for various psychiatric conditions in the past.(192)

11. TOURETTE SYNDROME

Tourette's syndrome (TS), a neurologic condition involving both motor and vocal tics, has recently been treated with DBS Few patients, however, have undergone DBS, and it remains unclear whether thalamic or pallidal targets (or a combination thereof) are preferable,(193) and both have been used.(194) In an effort to assess the impact of DBS for Tourette's Syndrome (TS) on cognition, Visser-Vandewalle and others(195) studied three patients whose electrodes were implanted at the level of the centromedian nucleus, substantia periventricularis, and nucleus ventrooralis internus. After chronic stimulation for a period of five years for the first patient, one year for the second patient, and eight months for the third patient, motor and vocal tics subsided completely. Neuropsychological test results were only reported for the first and third patient. No significant changes between pre- and postoperative cognitive test scores were noted in the first patient. Postoperative test scores with the third patient, however, demonstrated a decline in ability on timed tasks relative to baseline testing. Improvements were noted in both patients on verbal memory and facial recognition tests.

In a single TS patient, bilateral thalamic and/or GPi DBS at approximately 130 Hz resulted in a 70% improvement in the frequency of tics and self-injurious behavior,(196) and bilateral GPi DBS in another patient yielded a 73% reduction in vocal tics per minute after fourteen months of treatment.(197) When compared to preoperative cognitive testing, the patient in the former study demonstrated improvements in attention, episodic and working memory, and cognitive flexibility. The latter study noted that when compared to the baseline evaluation, cognitive test results did not change significantly on- or off-stimulation at the fourteen month study endpoint.

12. PERSISTENT VEGETATIVE AND MINIMALLY CONSCIOUS STATES

A recent single case report of thalamic DBS in a patient with minimally conscious state (MCS) after a traumatic brain injury more than six years previously (198) attracted a great deal of attention in the popular press. Although thalamic DBS (and DBS of the nucleus cuneiformis in the mesencephalic reticular formation) for persistent vegetative state (PVS) and MCS after traumatic brain injury, cerebrovascular accident and anoxia has been carried out in Japan since the 1980s (199-201), the recent case report provides an elegant multiple baseline design and detailed behavioral observation data not heretofore published. Although statistically significant improvements were observed in arousal level, motor control, and behavioral persistence, it is important to note that the patient remained dependent. This contrasts with some of the more optimistic findings reported by another group of researchers that had followed 21 cases of PVS and 5 cases of MCS for up to 10 years after DBS.(200). Although all of the 21 PVS cases remained bedridden, eight cases were reported to have emerged from VS and to have been able to communicate via speech or other responses (presumably motor). Of the five MCS cases, four emerged from the MCS and bedridden state and were able to "enjoy life in their own home." These findings must be interpreted with caution given the methodological limitations of the study.

The foregoing results provide an impetus for cautious optimism and further study, but, with little doubt, will also engender vociferous ethical debates.

13. OTHER CONDITIONS

Posterior hypothalamic DBS has recently been used to treat cluster headaches,(202) and posterior-medial hypothalamic stimulation was reported to decrease aggressive and disruptive behavior in two persons with mental retardation.(203) These studies, and studies using DBS for neuropathic pain,(204) have not reported neuropsychological outcomes. Tarsy and coworkers(205) reported that STN DBS in a patient with multiple system atrophy (MSA) developed speech problems (dysarthria), but neuropsychological outcome was not detailed. In a case with Huntington's disease, a single case study of GPI stimulation noted no neuropsychological changes 12 months after DBS, but details were not provided.(206) Antero-ventral pallidal stimulation in a case with Lesch-Nyhan disease was reported to improve self-injurious and aggressive behaviors. (207)

14. CONCLUSIONS

The past decade has seen a rapid expansion of medically refractory conditions and neuroanatomical structures targeted for DBS treatment, perhaps related to the success and relative safety of DBS demonstrated in movement disorders. A review of the literature and meta-analyses indicates DBS for movement disorders to be quite safe from a neurobehavioral standpoint (while improving motor symptoms and both the patient's and carepartner's quality of life). However, it is also clear that a small proportion of patients have moderate or severe neurobehavioral morbidity. If one combines the various cognitive and psychiatric morbidities reported across studies, it is probably reasonable to estimate that about 10% of patients with PD undergoing DBS will have one or more transient or permanent neurobehavioral adverse events. Deserving of urgent and detailed empirical investigation is the initial observation in a few small, uncontrolled studies that improvements in motor symptoms and quality of life may not necessarily translate into social (re)adjustment. Research will need to identify the patient, medico-surgical, and psychosocial factors that preclude some patients from demonstrating gains in occupational, interpersonal, familial, and marital functioning. It is likely, as has been shown in the epilepsy surgery literature, that symptomatic treatment success merely provides a new platform upon which to build or rebuild these social roles. Perhaps a much greater role of ancillary health services, such as speech therapy, occupational and physical therapy, neuropsychology, and psychotherapy needs to be contemplated if outcomes after DBS are to be optimized. Health care providers should not rely on subjective impression, spontaneous or solicited patient opinion, and cognitive and psychiatric screening measures to identify neurobehavioral and psychosocial issues. The recent publication of consensus statements on patient selection, treatment, and outcome evaluation(16, 208, 209) should facilitate greater uniformity in outcome reporting and identification of neurobehavioral risk. Although occurrence of dementia after DBS is very rare, recently published diagnostic criteria for dementia in PD (210) will likely facilitate more reliable identification of this condition. Treatment of dementia after DBS is not addressed in the literature, but it seems reasonable to select a therapeutic approach on an empirical basis. Specifically, comparing neuropsychological test performance on and off stimulation would provide an indication of whether stimulation has a contributory or causal role in cognitive dysfunction, allow one to weigh the relative cognitive cost and motor benefit of stimulation, and thereby facilitate the decision whether or not to turn off stimulation and proceed with the typical pharmacological management of PD dementia.

Urgently needed are carefully designed and executed multi-center studies of neurobehavioral outcomes. Despite an increasingly voluminous literature, the identification of reliable predictors and risk factors for neurobehavioral changes has received scant attention and proved elusive. Ethical concerns and seemingly intractable methodological limitations have impeded the conduct of sophisticated, controlled, blinded, comparative trials with large numbers of subjects needed to confidently quantify the incidence of various neurobehavioral changes and to isolate predictors of neurobehavioral and quality of life outcomes. To date, the literature does not allow one to conclude that stimulation per se is associated with neurobehavioral morbidity, though in some cases, there is a replicable effect on mood and cognition when stimulation is turned on and off. In the case of PD, and likely many of the emerging indications for DBS, neurobehavioral outcomes may be related to an interaction of the surgical procedure and stimulation as well as subsequent changes in medications, psychosocial factors and pre-operative vulnerability. Conclusions that DBS is neuropsychologically safe in conditions such as dystonia, depression, OCD, TS, epilepsy, MS and others must be considered highly preliminary until adequate, controlled trials are completed. Recent cognitive and social neuroscience studies of DBS, (211-215) particularly in the accompaniment of functional imaging (216, 217) suggest that DBS might be used as a vehicle to better understand the cognitive and behavioral role of the basal ganglia and other deep brain structures.

15. REFERENCES

1. R. Bartholow: Experimental Investigations into the Functions of the Human Brain *The American Journal of the Medical Sciences*, 67, 305-13 (1874)

2. V. Horsley: Remarks on ten consecutive cases of operations upon the brain and cranial cavity to illustrate the details and safety of the method employed. *British Medical Journal*, 1, 863-865 (1887)

3. J. M. Delgado: Permanent implantation of multilead electrodes in the brain. *Yale J Biol Med*, 24(5), 351-8 (1952)

4. R. G. Heath: Studies in schizophrenia: a multidisciplinary approach to mind-brain relationships. Harvard University Press, Cambridge, MA (1954)

5. J. L. Pool: Psychosurgery in older people. *J Am Geriatr Soc*, 2(7), 456-66 (1954)

6. C. W. Sem-Jacobsen: Depth electrographic stimulation and treatment of patients with Parkinson's disease including neurosurgical technique. *Acta Neurol Scand Suppl*, 13 Pt 1, 365-77 (1965)

7. P. Bechtereva, A. N. Bondartchuk, V. M. Smirnov, L. A. Meliutcheva and A. N. Shandurina: Method of electrostimulation of the deep brain structures in treatment of some chronic diseases. *Confinia Neurologica*, 37(1-3), 136-40 (1975)

8. J. Brice and L. McLellan: Suppression of intention tremor by contingent deep-brain stimulation. *Lancet*, 1(8180), 1221-2 (1980)

9. S. B. Wilkinson and A. I. Tröster: Surgical interventions in neurodegenerative disease: impact on memory and cognition. In: *Memory in neurodegenerative disease: biological, cognitive, and clinical perspectives*. Ed A. I. Tröster. Cambridge University Press, Cambridge, UK (1998)

10. M. S. Okun, R. L. Rodriguez, A. Mikos, K. Miller, I. Kellison, L. Kirsch-Darrow, D. P. Wint, U. Springer, H. H. Fernandez, K. D. Foote, G. Crucian and D. Bowers: Deep brain stimulation and the role of the neuropsychologist. *Clin Neuropsychol*, 21(1), 162-89 (2007)

11. E. Y. Uc and K. A. Follett: Deep brain stimulation in movement disorders. *Semin Neurol*, 27(2), 170-82 (2007)

12. P. J. Ford and C. S. Kubu: Stimulating debate: ethics in a multidisciplinary functional neurosurgery committee. *J Med Ethics*, 32(2), 106-9 (2006)

13. B. D. Greenberg: Deep brain stimulation in psychiatry. In: *Brain stimulation in psychiatric treatment*. Ed S. H. Lisanby. American Psychiatric Publishing, Washington, D.C. (2004)

14. J. J. Fins: From psychosurgery to neuromodulation and palliation: history's lessons for the ethical conduct and regulation of neuropsychiatric research. *Neurosurg Clin N Am*, 14(2), 303-19, ix-x (2003)

15. A. C. Heller, A. P. Amar, C. Y. Liu and M. L. Apuzzo: Surgery of the mind and mood: a mosaic of issues in time and evolution. *Neurosurgery*, 59(4), 720-33; discussion 733-9 (2006)

16. A. E. Lang, J. L. Houeto, P. Krack, C. Kubu, K. E. Lyons, E. Moro, W. Ondo, R. Pahwa, W. Poewe, A. I. Troster, R. Uitti and V. Voon: Deep brain stimulation:

preoperative issues. *Mov Disord*, 21 Suppl 14, S171-96 (2006)

17. A. Stefani, A. M. Lozano, A. Peppe, P. Stanzione, S. Galati, D. Tropepi, M. Pierantozzi, L. Brusa, E. Scarnati and P. Mazzone: Bilateral deep brain stimulation of the pedunculopontine and subthalamic nuclei in severe Parkinson's disease. *Brain*, 130(Pt 6), 1596-607 (2007)

18. P. Plaha, Y. Ben-Shlomo, N. K. Patel and S. S. Gill: Stimulation of the caudal zona incerta is superior to stimulation of the subthalamic nucleus in improving contralateral parkinsonism. *Brain*, 129(Pt 7), 1732-47 (2006)

19. K. Follett, F. Weaver, M. Stern, W. Marks, P. Hogarth, K. Holloway, J. Bronstein, J. Duda, S. Horn, E. Lai and A. Samii: Multisite randomized trial of deep brain stimulation. *Arch Neurol*, 62(10), 1643-4; author reply 1644-5 (2005)

20. D. Caparros-Lefebvre, S. Blond, N. Pécheux, F. Pasquier and H. Petit: Evaluation neuropsychologique avant et après stimulation thalamique chez 9 parkinsoniens. *Revue Neurologique*, 148(2), 117-22 (1992)

21. A. I. Tröster, J. A. Fields, S. B. Wilkinson, K. Busenbark, E. Miyawaki, J. Overman, R. Pahwa and W. C. Koller: Neuropsychological functioning before and after unilateral thalamic stimulating electrode implantation in Parkinson's disease [electronic manuscript]. *Neurosurgical Focus*, 2(3), Article 9 (pp. 1-6) (1997)

22. T. J. Loher, K. Gutbrod, N. L. Fravi, T. Pohle, J. M. Burgunder and J. K. Krauss: Thalamic stimulation for tremor. Subtle changes in episodic memory are related to stimulation per se and not to a microthalamotomy effect. *J Neurol*, 250(6), 707-13 (2003)

23. A. I. Tröster, S. B. Wilkinson, J. A. Fields, K. Miyawaki and W. C. Koller: 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 and Cognition*, 38(2), 125-49 (1998)

24. S. P. Woods, J. A. Fields, K. E. Lyons, W. C. Koller, S. B. Wilkinson, R. Pahwa and A. I. Tröster: Neuropsychological and quality of life changes following unilateral thalamic deep brain stimulation in Parkinson's disease: a 12-month follow-up. *Acta Neurochirurgica*, 143, 1273-8 (2001)

25. K. Straits-Tröster, J. A. Fields, S. B. Wilkinson, R. Pahwa, K. E. Lyons, W. C. Koller and A. I. Tröster: Health-related quality of life in Parkinson's disease after pallidotomy and deep brain stimulation. *Brain and Cognition*, 42(3), 399-416 (2000)

26. A. I. Tröster, J. A. Fields, S. B. Wilkinson, R. Pahwa, E. Miyawaki, K. E. Lyons and W. C. Koller: Unilateral

pallidal stimulation for Parkinson's disease: neurobehavioral functioning before and 3 months after electrode implantation. *Neurology*, 49(4), 1078-83 (1997)

27. G. Vingerhoets, C. van der Linden, E. Lannoo, V. Vandewalle, J. Caemaert, M. Wolters and D. Van den Abbeele: Cognitive outcome after unilateral pallidal stimulation in Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, 66(3), 297-304 (1999)

28. M. Merello, M. I. Nouzeilles, G. Kuzis, A. Cammarota, L. Sabe, O. Betti, S. Starkstein and R. Leiguarda: Unilateral radiofrequency lesion versus electrostimulation of posteroventral pallidum: a prospective randomized comparison. *Movement Disorders*, 14(1), 50-6 (1999)

29. C. Ardouin, B. Pillon, E. Peiffer, P. Bejjani, P. Limousin, P. Damier, I. Arnulf, A. L. Benabid, Y. Agid and P. Pollak: Bilateral subthalamic or pallidal stimulation for Parkinson's disease affects neither memory nor executive functions: a consecutive series of 62 patients. *Annals of Neurology*, 46(2), 217-23 (1999)

30. B. Pillon, C. Ardouin, P. Damier, P. Krack, J. L. Houeto, H. Klinger, A. M. Bonnet, P. Pollak, A. L. Benabid and Y. Agid: Neuropsychological changes between "off" and "on" STN or GPi stimulation in Parkinson's disease. *Neurology*, 55(3), 411-8 (2000)

31. J. Ghika, J. G. Villemure, H. Fankhauser, J. Favre, G. Assal and F. Ghika-Schmid: Efficiency and safety of bilateral contemporaneous pallidal stimulation (deep brain stimulation) in levodopa-responsive patients with Parkinson's disease with severe motor fluctuations: a 2-year follow-up review. *Journal of Neurosurgery*, 89(5), 713-8 (1998)

32. K. Dujardin, P. Krystkowiak, L. Defebvre, S. Blond and A. Destee: A case of severe dysexecutive syndrome consecutive to chronic bilateral pallidal stimulation. *Neuropsychologia*, 38(9), 1305-15 (2000)

33. L. L. Trepanier, R. Kumar, A. M. Lozano, A. E. Lang and J. A. Saint-Cyr: Neuropsychological outcome of GPi pallidotomy and GPi or STN deep brain stimulation in Parkinson's disease. *Brain and Cognition*, 42(3), 324-47 (2000)

34. J. Volkmann, N. Allert, J. Voges, V. Sturm, A. Schnitzler and H. J. Freund: Long-term results of bilateral pallidal stimulation in Parkinson's disease. *Ann Neurol*, 55(6), 871-5 (2004)

35. A. I. Tröster, S. P. Woods, J. A. Fields, C. Hanisch and W. W. Beatty: Declines in switching underlie verbal fluency changes after unilateral pallidal surgery in Parkinson's disease. *Brain and Cognition*, 50(2), 207-17 (2002)

36. J. A. Fields, A. I. Tröster, S. B. Wilkinson, R. Pahwa and W. C. Koller: Cognitive outcome following staged bilateral pallidal stimulation for the treatment of

Parkinson's disease. *Clinical Neurology and Neurosurgery*, 101(3), 182-8 (1999)

37. J. C. Rothlind, R. W. Cockshott, P. A. Starr and W. J. Marks: Neuropsychological performance following staged bilateral pallidal or subthalamic nucleus deep brain stimulation for Parkinson's disease. *J Int Neuropsychol Soc*, 13(1), 68-79 (2007)

38. J. A. Fields, A. I. Tröster, S. B. Wilkinson, K. E. Lyons, E. Miyawaki, R. Pahwa and W. C. Koller: Comparison of the cognitive safety of unilateral pallidal stimulation and pallidotomy [abstract]. *Neurology*, 50 (Suppl. 4), A389 (1998)

39. V. C. Anderson, K. J. Burchiel, P. Hogarth, J. Favre and J. P. Hammerstad: Pallidal vs subthalamic nucleus deep brain stimulation in Parkinson disease. *Arch Neurol*, 62(4), 554-60 (2005)

40. M. C. Rodriguez-Oroz, J. A. Obeso, A. E. Lang, J. L. Houeto, P. Pollak, S. Rehncrona, J. Kulisevsky, A. Albanese, J. Volkmann, M. I. Hariz, N. P. Quinn, J. D. Speelman, J. Guridi, I. Zamarbide, A. Gironell, J. Molet, B. Pascual-Sedano, B. Pidoux, A. M. Bonnet, Y. Agid, J. Xie, A. L. Benabid, A. M. Lozano, J. Saint-Cyr, L. Romito, M. F. Contarino, M. Scerrati, V. Fraix and N. Van Blercom: Bilateral deep brain stimulation in Parkinson's disease: a multicentre study with 4 years follow-up. *Brain* (2005)

41. J. Volkmann, N. Allert, J. Voges, P. H. Weiss, H.-J. Freund and V. Sturm: Safety and efficacy of pallidal or subthalamic nucleus stimulation in advanced PD. *Neurology*, 56(4), 548-51 (2001)

42. G. Vingerhoets, E. Lannoo, C. van der Linden, J. Caemaert, V. Vandewalle, D. van den Abbeele and M. Wolters: Changes in quality of life following unilateral pallidal stimulation in Parkinson's disease. *Journal of Psychosomatic Research*, 46(3), 247-55 (1999)

43. C. I. Higginson, J. A. Fields and A. I. Tröster: Which symptoms of anxiety diminish after surgical interventions for Parkinson's disease. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology*, 14(2), 117-21 (2001)

44. D. J. Burn and A. I. Troster: Neuropsychiatric complications of medical and surgical therapies for Parkinson's disease. *J Geriatr Psychiatry Neurol*, 17(3), 172-80 (2004)

45. V. Voon, C. Kubu, P. Krack, J. L. Houeto and A. I. Tröster: Deep brain stimulation: neuropsychological and neuropsychiatric issues. *Mov Disord*, 21 Suppl 14, S305-27 (2006)

46. V. Voon, E. Moro, J. A. Saint-Cyr, A. M. Lozano and A. E. Lang: Psychiatric symptoms following surgery for Parkinson's disease with an emphasis on subthalamic stimulation. In: *Behavioral Neurology of Movement*

Disorders Ed K. E. Anderson, W. J. Weiner & A. E. Lang. Lippincott, Williams & Wilkins, Philadelphia (2005)

47. E. Miyawaki, J. S. Perlmutter, A. I. Tröster, T. O. Videen and W. C. Koller: The behavioral complications of pallidal stimulation: a case report. *Brain and Cognition*, 42(3), 417-34 (2000)

48. M. Krause, W. Fogel, A. Heck, W. Hacke, M. Bonsanto, C. Trenkwalder and V. Tronnier: Deep brain stimulation for the treatment of Parkinson's disease: subthalamic nucleus versus globus pallidus internus. *Journal of Neurology, Neurosurgery, and Psychiatry*, 70(4), 464-70 (2001)

49. D. M. Roane, M. Yu, T. E. Feinberg and J. D. Rogers: Hypersexuality after pallidal surgery in Parkinson disease. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology*, 15(4), 247-51 (2002)

50. Y. Temel, A. Kessels, S. Tan, A. Topdag, P. Boon and V. Visser-Vandewalle: Behavioural changes after bilateral subthalamic stimulation in advanced Parkinson disease: a systematic review. *Parkinsonism Relat Disord*, 12(5), 265-72 (2006)

51. G. Kleiner-Fisman, D. N. Fisman, E. Sime, J. A. Saint-Cyr, A. M. Lozano and A. E. Lang: Long-term follow up of bilateral deep brain stimulation of the subthalamic nucleus in patients with advanced Parkinson disease. *Journal of Neurosurgery*, 99(3), 489-95 (2003)

52. G. Deuschl, C. Schade-Brittinger, P. Krack, J. Volkmann, H. Schafer, K. Botzel, C. Daniels, A. Deutschlander, U. Dillmann, W. Eisner, D. Gruber, W. Hamel, J. Herzog, R. Hilker, S. Klebe, M. Kloss, J. Koy, M. Krause, A. Kupsch, D. Lorenz, S. Lorenzl, H. M. Mehdorn, J. R. Moringlane, W. Oertel, M. O. Pinsker, H. Reichmann, A. Reuss, G. H. Schneider, A. Schnitzler, U. Steude, V. Sturm, L. Timmermann, V. Tronnier, T. Trottenberg, L. Wojtecki, E. Wolf, W. Poewe and J. Voges: A randomized trial of deep-brain stimulation for Parkinson's disease. *N Engl J Med*, 355(9), 896-908 (2006)

53. A. I. Tröster and J. A. Fields: The role of neuropsychological evaluation in the neurosurgical treatment of movement disorders. In: *Surgical Treatment of Parkinson's Disease and Other Movement Disorders*. Ed D. Tarsy, J. L. Vitek&A. M. Lozano. Humana Press, Totowa, NJ (2003)

54. S. P. Woods, J. D. Rippeth, E. Conover, C. L. Carey, T. D. Parsons and A. I. Tröster: Statistical power of studies examining the cognitive effects of subthalamic nucleus deep brain stimulation in Parkinson's disease. *The Clinical Neuropsychologist*, 20, 27-38 (2006)

55. M. Alegret, C. Junqué, F. Valldeoriola, P. Vendrell, M. Pilleri, J. Rumià and E. Tolosa: Effects of bilateral subthalamic stimulation on cognitive function in

Parkinson disease. *Archives of Neurology*, 58(8), 1223-7 (2001)

56. M. Alegret, F. Valldeoriola, M. Marti, M. Pilleri, C. Junque, J. Rumia and E. Tolosa: Comparative cognitive effects of bilateral subthalamic stimulation and subcutaneous continuous infusion of apomorphine in Parkinson's disease. *Mov Disord*, 19(12), 1463-9 (2004)

57. L. Castelli, P. Perozzo, M. Zibetti, B. Crivelli, U. Morabito, M. Lanotte, F. Cossa, B. Bergamasco and L. Lopiano: Chronic Deep Brain Stimulation of the Subthalamic Nucleus for Parkinson's Disease: Effects on Cognition, Mood, Anxiety and Personality Traits. *Eur Neurol*, 55(3), 136-144 (2006)

58. J. A. Saint-Cyr, L. L. Trépanier, R. Kumar, A. M. Lozano and A. E. Lang: Neuropsychological consequences of chronic bilateral stimulation of the subthalamic nucleus in Parkinson's disease. *Brain*, 123(Pt 10), 2091-2108 (2000)

59. H. M. Smeding, J. D. Speelman, M. Koning-Haanstra, P. R. Schuurman, P. Nijssen, T. van Laar and B. Schmand: Neuropsychological effects of bilateral STN stimulation in Parkinson disease: a controlled study. *Neurology*, 66(12), 1830-6 (2006)

60. L. Brusa, M. Pierantozzi, A. Peppe, M. G. Altibrandi, P. Giacomini, P. Mazzone and P. Stanzione: Deep brain stimulation (DBS) attentional effects parallel those of l-dopa treatment. *Journal of Neural Transmission*, 108(8-9), 1021-7 (2001)

61. M. F. Contarino, A. Daniele, A. H. Sibilia, L. M. Romito, A. R. Bentivoglio, G. Gainotti and A. Albanese: Cognitive outcome five years after bilateral chronic stimulation of subthalamic nucleus in patients with Parkinson's disease *Journal of Neurology, Neurosurgery, and Psychiatry* (in press)

62. K. Dujardin, L. Defebvre, P. Krystkowiak, S. Blond and A. Destée: Influence of chronic bilateral stimulation of the subthalamic nucleus on cognitive function in Parkinson's disease. *Journal of Neurology*, 248, 603-11 (2001)

63. T. Erola, P. Karinen, E. Heikkinen, J. Tuominen, T. Haapaniemi, J. Koivukangas and V. Myllyla: Bilateral subthalamic nucleus stimulation improves health-related quality of life in Parkinsonian patients. *Parkinsonism Relat Disord*, 11(2), 89-94 (2005)

64. A. Funkiewiez, C. Ardouin, E. Caputo, P. Krack, V. Fraix, H. Klinger, S. Chabardes, K. Foote, A. L. Benabid and P. Pollak: Long term effects of bilateral subthalamic nucleus stimulation on cognitive function, mood, and behaviour in Parkinson's disease. *J Neurol Neurosurg Psychiatry*, 75(6), 834-9 (2004)

65. A. Gironell, J. Kulisevsky, L. Rami, N. Fortuny, C. Garcia-Sanchez and B. Pascual-Sedano: Effects of

pallidotomy and bilateral subthalamic stimulation on cognitive function in Parkinson disease. A controlled comparative study. *J Neurol*, 250(8), 917-23 (2003)

66. M. Jahanshahi, C. M. Ardouin, R. G. Brown, J. C. Rothwell, J. Obeso, A. Albanese, M. C. Rodriguez-Oroz, E. Moro, A. L. Benabid, P. Pollak and P. Limousin-Dowsey: The impact of deep brain stimulation on executive function in Parkinson's disease. *Brain*, 123(Pt 6), 1142-54 (2000)

67. R. Moretti, P. Torre, R. M. Antonello, L. Capus, M. Gioulis, S. Z. Marsala, G. Cazzato and A. Bava: Effects on cognitive abilities following subthalamic nucleus stimulation in Parkinson's disease. *European Journal of Neurology*, 8(6), 726-7 (2001)

68. R. Moretti, P. Torre, R. M. Antonello, L. Capus, S. Z. Marsala, T. Cattaruzza, G. Cazzato and A. Bava: Neuropsychological changes after subthalamic nucleus stimulation: a 12 month follow-up in nine patients with Parkinson's disease. *Parkinsonism Relat Disord*, 10(2), 73-9 (2003)

69. C. E. Morrison, J. C. Borod, M. F. Brin, S. A. Raskin, I. M. Germano, D. J. Weisz and C. W. Olanow: A program for neuropsychological investigation of deep brain stimulation (PNIDBS) in movement disorder patients: development, feasibility, and preliminary data. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology*, 13(3), 204-19 (2000)

70. C. E. Morrison, J. C. Borod, K. Perrine, A. Beric, M. F. Brin, A. Rezai, P. Kelly, D. Sterio, I. Germano, D. Weisz and C. W. Olanow: Neuropsychological functioning following bilateral subthalamic nucleus stimulation in Parkinson's disease. *Arch Clin Neuropsychol*, 19(2), 165-81 (2004)

71. P. Perozzo, M. Rizzone, B. Bergamasco, L. Castelli, M. Lanotte, A. Tavella, E. Torre and L. Lopiano: Deep brain stimulation of the subthalamic nucleus in Parkinson's disease: comparison of pre- and postoperative neuropsychological evaluation. *Journal of the Neurological Sciences*, 192(1-2), 9-15 (2001)

72. H. M. Smeding, R. A. Esselink, B. Schmand, M. Koning-Haanstra, I. Nijhuis, E. M. Wijnalda and J. D. Speelman: Unilateral pallidotomy versus bilateral subthalamic nucleus stimulation in PD--a comparison of neuropsychological effects. *J Neurol*, 252(2), 176-82 (2005)

73. B. M. Whelan, B. E. Murdoch, D. G. Theodoros, B. Hall and P. Silburn: Defining a role for the subthalamic nucleus within operative theoretical models of subcortical participation in language. *J Neurol Neurosurg Psychiatry*, 74(11), 1543-50 (2003)

74. K. Witt, U. Pulkowski, J. Herzog, D. Lorenz, W. Hamel, G. Deuschl and P. Krack: Deep brain stimulation of the subthalamic nucleus improves cognitive flexibility but impairs response inhibition in Parkinson disease. *Arch Neurol*, 61(5), 697-700 (2004)

75. D. Drapier, S. Drapier, P. Sauleau, C. Haegelen, S. Raoul, I. Biseul, J. Peron, F. Lallement, I. Rivier, J. M. Reymann, G. Edan, M. Verin and B. Millet: Does subthalamic nucleus stimulation induce apathy in Parkinson's disease? *J Neurol*, 253(8), 1083-91 (2006)

76. D. De Gaspari, C. Siri, A. Landi, R. Cilia, A. Bonetti, F. Natuzzi, L. Morgante, C. B. Mariani, E. Sganzerla, G. Pezzoli and A. Antonini: Clinical and neuropsychological follow up at 12 months in patients with complicated Parkinson's disease treated with subcutaneous apomorphine infusion or deep brain stimulation of the subthalamic nucleus. *J Neurol Neurosurg Psychiatry*, 77(4), 450-3 (2006)

77. B. J. Bordini, A. Garg, C. L. Gallagher, B. Bell and P. C. Garell: Neuropsychological Effects of Bilateral Deep Brain Stimulation of the Subthalamic Nucleus in Parkinson's Disease. *Stereotact Funct Neurosurg*, 85(2-3), 113-120 (2007)

78. J. L. Slowinski, J. D. Putzke, R. J. Uitti, J. A. Lucas, M. F. Turk, B. A. Kall and R. E. Wharen: Unilateral deep brain stimulation of the subthalamic nucleus for Parkinson disease. *J Neurosurg*, 106(4), 626-32 (2007)

79. R. Cilia, C. Siri, G. Marotta, D. D. Gaspari, A. Landi, C. B. Mariani, R. Benti, I. U. Isaias, F. Vergani, G. Pezzoli and A. Antonini: Brain networks underlining verbal fluency decline during STN-DBS in Parkinson's disease: An ECD-SPECT study. *Parkinsonism Relat Disord*, 13(5), 290-4 (2007)

80. T. D. Parsons, S. A. Rogers, A. J. Braaten, S. P. Woods and A. I. Troster: Cognitive sequelae of subthalamic nucleus deep brain stimulation in Parkinson's disease: a meta-analysis. *Lancet Neurol*, 5(7), 578-88 (2006)

81. Y. Temel, A. Blokland, H. W. Steinbusch and V. Visser-Vandewalle: The functional role of the subthalamic nucleus in cognitive and limbic circuits. *Prog Neurobiol*, 76(6), 393-413 (2005)

82. J. S. Perlmutter and J. W. Mink: Deep brain stimulation. *Annu Rev Neurosci*, 29, 229-57 (2006)

83. T. Wichmann and M. R. Delong: Deep brain stimulation for neurologic and neuropsychiatric disorders. *Neuron*, 52(1), 197-204 (2006)

84. A. Sudhyadhom, F. J. Bova, K. D. Foote, C. A. Rosado, L. Kirsch-Darrow and M. S. Okun: Limbic, associative, and motor territories within the targets for deep brain stimulation: potential clinical implications. *Curr Neurol Neurosci Rep*, 7(4), 278-89 (2007)

85. H. M. Smeding, P. van den Munckhof, R. A. Esselink, B. Schmand, P. R. Schuurman and J. D. Speelman: Reversible cognitive decline after DBS STN in PD and displacement of electrodes. *Neurology*, 68(15), 1235-6 (2007)

86. M. P. Perriol, P. Krystkowiak, L. Defebvre, S. Blond, A. Destee and K. Dujardin: Stimulation of the subthalamic nucleus in Parkinson's disease: cognitive and affective changes are not linked to the motor outcome. *Parkinsonism Relat Disord*, 12(4), 205-10 (2006)

87. L. Mallet, M. Schupbach, K. N'Diaye, P. Remy, E. Bardinet, V. Czernecki, M. L. Welter, A. Pelissolo, M. Ruberg, Y. Agid and J. Yelnik: Stimulation of subterritories of the subthalamic nucleus reveals its role in the integration of the emotional and motor aspects of behavior. *Proc Natl Acad Sci U S A*, 104(25), 10661-6 (2007)

88. A. Hristova, K. Lyons, A. I. Tröster, R. Pahwa, S. B. Wilkinson and W. C. Koller: Effect and time course of deep brain stimulation of the globus pallidus and subthalamus on motor features of Parkinson's disease. *Clinical Neuropharmacology*, 23(4), 208-11 (2000)

89. P. Francel, K. Ryder, J. Wetmore, A. Stevens, K. Bharucha, W. W. Beatty and J. Scott: Deep brain stimulation for Parkinson's disease: association between stimulation parameters and cognitive performance. *Stereotact Funct Neurosurg*, 82(4), 191-3 (2004)

90. M. Jahanshahi, R. G. Brown, J. C. Rothwell, P. Pollak and P. Limousin: Subthalamic nucleus (STN) and globus pallidus (GPi) stimulation in Parkinson's disease (PD): II. effects on executive function and working memory [abstract]. *Movement Disorders*, 12 (Suppl. 1), 130 (1997)

91. T. Hershey, F. J. Revilla, A. Wernle, P. S. Gibson, J. L. Dowling and J. S. Perlmutter: Stimulation of STN impairs aspects of cognitive control in PD. *Neurology*, 62(7), 1110-4 (2004)

92. D. Page and M. Jahanshahi: Deep brain stimulation of the subthalamic nucleus improves set shifting but does not affect dual task performance in Parkinson's disease. *IEEE Trans Neural Syst Rehabil Eng*, 15(2), 198-206 (2007)

93. L. Wojtecki, L. Timmermann, S. Jorgens, M. Sudmeyer, M. Maarouf, H. Treuer, J. Gross, R. Lehrke, A. Koulousakis, J. Voges, V. Sturm and A. Schnitzler: Frequency-dependent reciprocal modulation of verbal fluency and motor functions in subthalamic deep brain stimulation. *Arch Neurol*, 63(9), 1273-6 (2006)

94. M. I. Hariz, F. Johansson, P. Shamsgovara, E. Johansson, G. M. Hariz and M. Fagerlund: 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. *Movement Disorders*, 15(1), 136-9 (2000)

95. F. Valldeoriola, E. Tolosa, M. Alegret, E. Tolosa, M. J. Rey, O. Morsi, M. Pilleri and J. Rumia: Cognitive changes in Parkinson's disease during subthalamic stimulation: a clinicopathologic study. *J Neurol Neurosurg Psychiatry*, 77(4), 565-6 (2006)

96. B. Jarraya, A. M. Bonnet, C. Duyckaerts, J. L. Houeto, P. Cornu, J. J. Hauw and Y. Agid: Parkinson's disease, subthalamic stimulation, and selection of candidates: a pathological study. *Mov Disord*, 18(12), 1517-20 (2003)

97. A. I. Benabid, A. Koudsié, A. Benazzouz, D. Hoffmann, V. Fraix, S. Chabardes, J. F. Le Bas and P. Pollack: Neurosurgical therapy in Parkinson's disease. In: *Mental dysfunction in Parkinson's disease II*. Ed E. C. Wolters, P. Scheltens&H. W. Berendse. Academic Pharmaceutical Productions, Utrecht, The Netherlands (1999)

98. F. Ory-Magne, C. Brefel-Courbon, M. Simonetta-Moreau, N. Fabre, J. A. Lotterie, P. Chaynes, I. Berry, Y. Lazorthes and O. Rascol: Does ageing influence deep brain stimulation outcomes in Parkinson's disease? *Mov Disord*, 22(10), 1457-63 (2007)

99. S. Aybek, A. Gronchi-Perrin, A. Berney, S. C. Chiuve, J. G. Villemure, P. R. Burkhard and F. J. Vingerhoets: Long-term cognitive profile and incidence of dementia after STN-DBS in Parkinson's disease. *Mov Disord*, 22(7), 974-81 (2007)

100. E. B. Montgomery, Jr.: Effect of subthalamic nucleus stimulation patterns on motor performance in Parkinson's disease. *Parkinsonism Relat Disord*, 11(3), 167-71 (2005)

101. G. M. Schulz and M. K. Grant: Effects of speech therapy and pharmacologic and surgical treatments on voice and speech in Parkinson's disease: a review of the literature. *J Commun Disord*, 33(1), 59-88 (2000)

102. D. Joel and I. Weiner: The connections of the primate subthalamic nucleus: indirect pathways and the open-interconnected scheme of basal ganglia-thalamocortical circuitry. *Brain Research. Brain Research Reviews*, 23(1-2), 62-78 (1997)

103. S. Pinto, S. Thobois, N. Costes, D. Le Bars, A. L. Benabid, E. Broussolle, P. Pollak and M. Gentil: Subthalamic nucleus stimulation and dysarthria in Parkinson's disease: a PET study. *Brain* (2004)

104. M. Gentil, P. Garcia-Ruiz, P. Pollak and A. L. Benabid: Effect of stimulation of the subthalamic nucleus on oral control of patients with parkinsonism. *Journal of Neurology, Neurosurgery, and Psychiatry*, 67(3), 329-33 (1999)

105. M. Gentil, S. Pinto, P. Pollak and A.-L. Benabid: Effect of bilateral stimulation of the subthalamic nucleus on parkinsonian dysarthria. *Brain and Language*, 85(2), 190-6 (2003)

106. M. Rousseaux, P. Krystkowiak, O. Kozlowski, C. Ozsancak, S. Blond and A. Destee: Effects of subthalamic nucleus stimulation on parkinsonian dysarthria and speech intelligibility. *J Neurol*, 251(3), 327-34 (2004)

107. P. Santens, M. De Letter, J. Van Borsel, J. De Reuck and J. Caemaert: Lateralized effects of subthalamic nucleus

stimulation on different aspects of speech in Parkinson's disease. *Brain Lang*, 87(2), 253-8 (2003)

108. R. Moretti, P. Torre, R. M. Antonello, L. Capus, M. Gioulis, S. Zambito Marsala, G. Cazzato and A. Bava: 'Speech initiation hesitation' following subthalamic nucleus stimulation in a patient with Parkinson's disease. *Eur Neurol*, 49(4), 251-3 (2003)

109. S. Pinto, M. Gentil, P. Krack, P. Sauleau, V. Fraix, A. L. Benabid and P. Pollak: Changes induced by levodopa and subthalamic nucleus stimulation on parkinsonian speech. *Mov Disord*, 20(11), 1507-15 (2005)

110. A. L. Tornqvist, L. Schalen and S. Rehncrona: Effects of different electrical parameter settings on the intelligibility of speech in patients with Parkinson's disease treated with subthalamic deep brain stimulation. *Mov Disord*, 20(4), 416-23 (2005)

111. S. Zanini, A. Melatini, L. Capus, M. Gioulis, A. Vassallo and A. Bava: Language recovery following subthalamic nucleus stimulation in Parkinson's disease. *Neuroreport*, 14(3), 511-6 (2003)

112. M. K. York, H. S. Levin, R. G. Grossman, E. C. Lai and J. K. Krauss: Clustering and switching in phonemic fluency following pallidotomy for the treatment of Parkinson's disease. *Journal of Clinical and Experimental Neuropsychology*, 25(1), 110-21 (2003)

113. D. De Gaspari, C. Siri, M. Di Gioia, A. Antonini, V. Isella, A. Pizzolato, A. Landi, F. Vergani, S. M. Gaini, I. M. Appollonio and G. Pezzoli: Clinical correlates and cognitive underpinnings of verbal fluency impairment after chronic subthalamic stimulation in Parkinson's disease. *Parkinsonism Relat Disord*, 12(5), 289-95 (2006)

114. G. Kleiner-Fisman, J. Herzog, D. N. Fisman, F. Tamma, K. E. Lyons, R. Pahwa, A. E. Lang and G. Deuschl: Subthalamic nucleus deep brain stimulation: summary and meta-analysis of outcomes. *Mov Disord*, 21 Suppl 14, S290-304 (2006)

115. J. Gan, J. Xie-Brustolin, P. Mertens, G. Polo, H. Klinger, H. Mollion, I. Benatru, E. Henry, E. Broussolle and S. Thobois: Bilateral subthalamic nucleus stimulation in advanced Parkinson's disease: three years follow-up. *J Neurol*, 254(1), 99-106 (2007)

116. J. Voges, Y. Waerzeggers, M. Maarouf, R. Lehrke, A. Koulousakis, D. Lenartz and V. Sturm: Deep-brain stimulation: long-term analysis of complications caused by hardware and surgery--experiences from a single centre. *J Neurol Neurosurg Psychiatry*, 77(7), 868-72 (2006)

117. J. L. Houeto, V. Mesnage, L. Mallet, B. Pillon, M. Gargiulo, S. T. Du Moncel, A. M. Bonnet, B. Pidoux, D. Dormont, P. Cornu and Y. Agid: Behavioural disorders, Parkinson's disease and subthalamic stimulation. *Journal of Neurology, Neurosurgery, and Psychiatry*, 72(6), 701-707 (2002)

118. N. J. Diederich, F. Alesch and C. G. Goetz: Visual hallucinations induced by deep brain stimulation in Parkinson's disease. *Clinical Neuropharmacology*, 23(5), 287-9 (2000)

119. M. S. Okun, D. V. Raju, B. L. Walter, J. L. Juncos, M. R. DeLong, K. Heilman, W. M. McDonald and J. L. Vitek: Pseudobulbar crying induced by stimulation in the region of the subthalamic nucleus. *J Neurol Neurosurg Psychiatry*, 75(6), 921-3 (2004)

120. R. Kumar, A. M. Lozano, E. Sime, E. Halket and A. E. Lang: Comparative effects of unilateral and bilateral subthalamic nucleus deep brain stimulation. *Neurology*, 53(3), 561-6 (1999)

121. A. L. Benabid, A. Koudsié, A. Benazzouz, L. Vercueil, V. Fraix, S. Chabardes, J. F. LeBas and P. Pollak: Deep brain stimulation of the corpus luysi (subthalamic nucleus) and other targets in Parkinson's disease. Extension to new indications such as dystonia and epilepsy. *Journal of Neurology*, 248 (Suppl. 3), 37-47 (2001)

122. B. P. Bejjani, P. Damier, I. Arnulf, L. Thivard, A. M. Bonnet, D. Dormont, P. Cornu, B. Pidoux, Y. Samson and Y. Agid: Transient acute depression induced by high-frequency deep-brain stimulation. *New England Journal of Medicine*, 340(19), 1476-80 (1999)

123. J. L. Houeto, P. Damier, P. B. Bejjani, C. Staedler, A. M. Bonnet, I. Arnulf, B. Pidoux, D. Dormont, P. Cornu and Y. Agid: Subthalamic stimulation in Parkinson disease: a multidisciplinary approach. *Archives of Neurology*, 57(4), 461-5 (2000)

124. M. S. Okun, J. Green, R. Saben, R. Gross, K. D. Foote and J. L. Vitek: Mood changes with deep brain stimulation of STN and GPi: results of a pilot study. *J Neurol Neurosurg Psychiatry*, 74(11), 1584-6 (2003)

125. S. Y. Chen, S. Z. Lin and T. W. Lee: Subthalamic nucleus stimulation and the development of delusion. *J Psychiatr Res*, 38(6), 637-8 (2004)

126. B. P. Bejjani, J. L. Houeto, M. Hariz, J. Yelnik, V. Mesnage, A. M. Bonnet, B. Pidoux, D. Dormont, P. Cornu and Y. Agid: Aggressive behavior induced by intraoperative stimulation in the triangle of Sano. *Neurology*, 59(9), 1425-7 (2002)

127. M. Sensi, R. Eleopra, M. A. Cavallo, E. Sette, P. Milani, R. Quatrale, J. G. Capone, V. Tugnoli, M. R. Tola, E. Granieri and P. G. Data: Explosive-aggressive behavior related to bilateral subthalamic stimulation. *Parkinsonism Relat Disord*, 10(4), 247-51 (2004)

128. K. Kalteis, H. Standhardt, I. Kryspin-Exner, T. Brucke, D. Volc and F. Alesch: Influence of bilateral Stn-stimulation on psychiatric symptoms and psychosocial functioning in patients with Parkinson's disease. *J Neural Transm*, 113(9), 1191-206 (2006)

129. V. Czernecki, B. Pillon, J. L. Houeto, M. L. Welter, V. Mesnage, Y. Agid and B. Dubois: Does bilateral stimulation of the subthalamic nucleus aggravate apathy in Parkinson's disease? *J Neurol Neurosurg Psychiatry*, 76(6), 775-9 (2005)

130. V. Voon, J. Saint-Cyr, A. M. Lozano, E. Moro, Y. Y. Poon and A. E. Lang: Psychiatric symptoms in patients with Parkinson disease presenting for deep brain stimulation surgery. *J Neurosurg*, 103(2), 246-51 (2005)

131. H. M. Smeding, A. E. Goudriaan, E. M. Foncke, P. R. Schuurman, J. D. Speelman and B. Schmand: Pathological gambling after bilateral subthalamic nucleus stimulation in Parkinson disease. *J Neurol Neurosurg Psychiatry*, 78(5), 517-9 (2007)

132. C. Ardouin, V. Voon, Y. Worbe, N. Abouazar, V. Czernecki, H. Hosseini, A. Pelissolo, E. Moro, E. Lhommee, A. E. Lang, Y. Agid, A. L. Benabid, P. Pollak, L. Mallet and P. Krack: Pathological gambling in Parkinson's disease improves on chronic subthalamic nucleus stimulation. *Mov Disord*, 21(11), 1941-6 (2006)

133. A. Diamond and J. Jankovic: The effect of deep brain stimulation on quality of life in movement disorders. *J Neurol Neurosurg Psychiatry*, 76(9), 1188-93 (2005)

134. E. Lezcano, J. C. Gomez-Esteban, J. J. Zarranz, I. Lambarri, P. Madoz, G. Bilbao, I. Pomposo and J. Garibi: Improvement in quality of life in patients with advanced Parkinson's disease following bilateral deep-brain stimulation in subthalamic nucleus. *Eur J Neurol*, 11(7), 451-4 (2004)

135. S. Drapier, S. Raoul, D. Drapier, E. Leray, F. Lallement, I. Rivier, P. Sauleau, Y. Lajat, G. Edan and M. Verin: Only physical aspects of quality of life are significantly improved by bilateral subthalamic stimulation in Parkinson's disease. *J Neurol*, 252(5), 583-8 (2005)

136. P. Martínez-Martín, F. Valldeoriola, E. Tolosa, M. Pilleri, J. L. Molinuevo, J. Rumià and E. Ferrer: Bilateral subthalamic nucleus stimulation and quality of life in advanced Parkinson's disease. *Movement Disorders*, 17(2), 372-7 (2002)

137. A. Siderowf, J. L. Jaggi, S. X. Xie, C. Loveland-Jones, L. Leng, H. Hurtig, A. Colcher, M. Stern, K. L. Chou, G. Liang, H. Maccarone, T. Simuni and G. Baltuch: Long-term effects of bilateral subthalamic nucleus stimulation on health-related quality of life in advanced Parkinson's disease. *Mov Disord*, 21(6), 746-753 (2006)

138. E. Lagrange, P. Krack, E. Moro, C. Ardouin, N. Van Blercom, S. Chabardes, A. L. Benabid and P. Pollak: Bilateral subthalamic nucleus stimulation improves health-related quality of life in PD. *Neurology*, 59(12), 1976-8 (2002)

139. P. P. Derost, L. Ouchchane, D. Morand, M. Ulla, P. M. Llorca, M. Barget, B. Debilly, J. J. Lemaire and F. Durif: Is DBS-STN appropriate to treat severe Parkinson disease in an elderly population? *Neurology*, 68(17), 1345-55 (2007)

140. K. E. Lyons and R. Pahwa: Long-term benefits in quality of life provided by bilateral subthalamic stimulation in patients with Parkinson disease. *J Neurosurg*, 103(2), 252-5 (2005)

141. A. I. Tröster, J. A. Fields, S. Wilkinson, R. Pahwa, W. C. Koller and K. E. Lyons: Effect of motor improvement on quality of life following subthalamic stimulation is mediated by changes in depressive symptomatology. *Stereotact Funct Neurosurg*, 80(1-4), 43-7 (2003)

142. J. L. Houeto, L. Mallet, V. Mesnage, S. Tezenas du Montcel, C. Behar, M. Gargiulo, F. Torny, A. Pelissolo, M. L. Welter and Y. Agid: Subthalamic stimulation in Parkinson disease: behavior and social adaptation. *Arch Neurol*, 63(8), 1090-5 (2006)

143. M. Schupbach, M. Gargiulo, M. L. Welter, L. Mallet, C. Behar, J. L. Houeto, D. Maltete, V. Mesnage and Y. Agid: Neurosurgery in Parkinson disease: a distressed mind in a repaired body? *Neurology*, 66(12), 1811-6 (2006)

144. P. Perozzo, M. Rizzone, B. Bergamasco, L. Castelli, M. Lanotte, A. Tavella, E. Torre and L. Lopiano: Deep brain stimulation of subthalamic nucleus: behavioural modifications and familiar relations. *Neurological Sciences*, 22(1), 81-2 (2001)

145. R. Kumar, A. M. Lozano, E. Sime and A. E. Lang: Long-term follow-up of thalamic deep brain stimulation for essential and parkinsonian tremor. *Neurology*, 61(11), 1601-4 (2003)

146. P. Limousin, J. D. Speelman, F. Gielen and M. Janssens: Multicentre European study of thalamic stimulation in parkinsonian and essential tremor. *Journal of Neurology, Neurosurgery, and Psychiatry*, 66(3), 289-96 (1999)

147. R. Pahwa, K. L. Lyons, S. B. Wilkinson, M. A. Carpenter, A. I. Tröster, J. P. Searl, J. Overman, S. Pickering and W. C. Koller: Bilateral thalamic stimulation for the treatment of essential tremor. *Neurology*, 53(7), 1447-50 (1999)

148. S. Rehncrona, B. Johnels, H. Widner, A. L. Tornqvist, M. Hariz and O. Sydow: Long-term efficacy of thalamic deep brain stimulation for tremor: double-blind assessments. *Mov Disord*, 18(2), 163-70 (2003)

149. P. Plaha, N. K. Patel and S. S. Gill: Stimulation of the subthalamic region for essential tremor. *J Neurosurg*, 101(1), 48-54 (2004)

150. M. Kitagawa, J. Murata, S. Kikuchi, Y. Sawamura, H. Saito, H. Sasaki and K. Tashiro: Deep brain stimulation of subthalamic area for severe proximal tremor. *Neurology*, 55(1), 114-6 (2000)

151. J. Murata, M. Kitagawa, H. Uesugi, H. Saito, Y. Iwaski, S. Kikuchi, K. Tashiro and Y. Sawamura: Electrical stimulation of the posterior subthalamic area for the treatment of intractable proximal tremor. *J Neurosurg*, 99(4), 708-15 (2003)

152. S. Blond, D. Caparros-Lefebvre, F. Parker, R. Assaker, H. Petit, J.-D. Guieu and J.-L. Christiaens: Control of tremor and involuntary movement disorders by chronic stereotactic stimulation of the ventral intermediate thalamic nucleus. *Journal of Neurosurgery*, 77(1), 62-8 (1992)

153. A. I. Tröster, J. A. Fields, R. Pahwa, S. B. Wilkinson, K. A. Straits-Tröster, K. Lyons, J. Kieltyka and W. C. Koller: Neuropsychological and quality of life outcome after thalamic stimulation for essential tremor. *Neurology*, 53(8), 1774-80 (1999)

154. J. A. Fields, A. I. Tröster, S. P. Woods, C. I. Higginson, S. B. Wilkinson, K. E. Lyons, W. C. Koller and R. Pahwa: Neuropsychological and quality of life outcomes 12 months after unilateral thalamic stimulation for essential tremor. *Journal of Neurology, Neurosurgery, and Psychiatry*, 74(3), 305-311 (2003)

155. J. A. Lucas, J. Rippeth, R. Uitti, A. Obwegeser and R. Wharen: Cognitive, motor, and mood-related effects of left thalamic stimulation in the treatment of parkinsonian and essential tremor [abstract]. *Journal of the International Neuropsychological Society*, 6(4), 392 (2000)

156. S. P. Woods, J. A. Fields, K. E. Lyons, R. Pahwa and A. I. Tröster: Pulse width is associated with cognitive decline after thalamic stimulation for essential tremor. *Parkinsonism and Related Disorders*, 9, 295-300 (2003)

157. W. Ondo, J. Jankovic, K. Schwartz, M. Almaguer and R. K. Simpson: Unilateral thalamic deep brain stimulation for refractory essential tremor and Parkinson's disease tremor. *Neurology*, 51(4), 1063-9 (1998)

158. J. A. Bryant, A. De Salles, C. Cabatan, R. Frysinger, E. Behnke and J. Bronstein: The impact of thalamic stimulation on activities of daily living for essential tremor. *Surg Neurol*, 59(6), 479-84; discussion 484-5 (2003)

159. K. E. Lyons, R. Pahwa, K. L. Busenbark, A. I. Tröster, S. Wilkinson and W. C. Koller: Improvements in daily functioning after deep brain stimulation of the thalamus for intractable tremor. *Movement Disorders*, 13(4), 690-2 (1998)

160. O. Sydow, S. Thobois, F. Alesch and J. D. Speelman: Multicentre European study of thalamic stimulation in essential tremor: a six year follow up. *Journal of Neurology, Neurosurgery, and Psychiatry*, 74(10), 1387-91 (2003)

161. I. S. Cooper, A. R. Upton and I. Amin: Reversibility of chronic neurologic deficits. Some effects of electrical stimulation of the thalamus and internal capsule in man. *Applied Neurophysiology*, 43(3-5), 244-58 (1980)

162. O. J. Andy: Thalamic stimulation for control of movement disorders. *Applied Neurophysiology*, 46(1-4), 107-11 (1983)

163. M. Vidailhet, L. Vercueil, J. L. Houeto, P. Krystkowiak, A. L. Benabid, P. Cornu, C. Lagrange, S. Tezenas du Montcel, D. Dormont, S. Grand, S. Blond, O. Detante, B. Pillon, C. Ardouin, Y. Agid, A. Destee and P. Pollak: Bilateral deep-brain stimulation of the globus pallidus in primary generalized dystonia. *N Engl J Med*, 352(5), 459-67 (2005)

164. A. Kupsch, R. Benecke, J. Muller, T. Trottenberg, G. H. Schneider, W. Poewe, W. Eisner, A. Wolters, J. U. Muller, G. Deuschl, M. O. Pinsker, I. M. Skogseid, G. K. Roeste, J. Vollmer-Haase, A. Brentrup, M. Krause, V. Tronnier, A. Schnitzler, J. Voges, G. Nikkhah, J. Vesper, M. Naumann and J. Volkmann: Pallidal deep-brain stimulation in primary generalized or segmental dystonia. *N Engl J Med*, 355(19), 1978-90 (2006)

165. T. D. Hälbig, D. Gruber, U. A. Kopp, G. H. Schneider, T. Trottenberg and A. Kupsch: Pallidal stimulation in dystonia: effects on cognition, mood, and quality of life. *J Neurol Neurosurg Psychiatry*, 76(12), 1713-6 (2005)

166. B. Pillon, C. Ardouin, K. Dujardin, P. Vittini, A. Pelissolo, O. Cottencin, L. Vercueil, J. L. Houeto, P. Krystkowiak, Y. Agid, A. Destee, P. Pollak and M. Vidailhet: Preservation of cognitive function in dystonia treated by pallidal stimulation. *Neurology*, 66(10), 1556-8 (2006)

167. G. Kleiner-Fisman, G. S. Liang, P. J. Moberg, A. C. Ruocco, H. I. Hurtig, G. H. Baltuch, J. L. Jaggi and M. B. Stern: Subthalamic nucleus deep brain stimulation for severe idiopathic dystonia: impact on severity, neuropsychological status, and quality of life. *J Neurosurg*, 107(1), 29-36 (2007)

168. C. E. Polkey: Brain stimulation in the treatment of epilepsy. *Expert Rev Neurother*, 4(6), 965-72 (2004)

169. W. H. Theodore and R. S. Fisher: Brain stimulation for epilepsy. *Lancet Neurol*, 3(2), 111-8 (2004)

170. I. S. Cooper, I. Amin, A. Upton, M. Riklan, S. Watkins and L. McLellan: Safety and efficacy of chronic stimulation. *Neurosurgery*, 1(2), 203-5 (1977)

171. I. S. Cooper and A. R. Upton: Effects of cerebellar stimulation on epilepsy, the EEG and cerebral palsy in man. *Electroencephalogr Clin Neurophysiol Suppl*(34), 349-54 (1978)

172. M. Hodaie, R. A. Wennberg, J. O. Dostrovsky and A. M. Lozano: Chronic anterior thalamus stimulation for intractable epilepsy. *Epilepsia*, 43(6), 603-8 (2002)

173. N. M. Graves and R. S. Fisher: Neurostimulation for epilepsy, including a pilot study of anterior nucleus stimulation. *Clin Neurosurg*, 52, 127-34 (2005)

174. R. S. Fisher, S. Uematsu, G. L. Krauss, B. J. Cysyk, R. McPherson, R. P. Lesser, B. Gordon, P. Schwerdt and M. Rise: Placebo-controlled pilot study of centromedian thalamic stimulation in treatment of intractable seizures. *Epilepsia*, 33(5), 841-51 (1992)

175. J. F. Tellez-Zenteno, R. S. McLachlan, A. Parrent, C. S. Kubu and S. Wiebe: Hippocampal electrical stimulation in mesial temporal lobe epilepsy. *Neurology*, 66(10), 1490-4 (2006)

176. T. P. Duprez, B. A. Serieh and C. Raftopoulos: Absence of memory dysfunction after bilateral mammillary body and mammillothalamic tract electrode implantation: preliminary experience in three patients. *AJNR Am J Neuroradiol*, 26(1), 195-7; author reply 197-8 (2005)

177. R. V. Patwardhan, A. Minagar, R. E. Kelley and A. Nanda: Neurosurgical treatment of multiple sclerosis. *Neurol Res*, 28(3), 320-5 (2006)

178. K. D. Foote, P. Seignourel, H. H. Fernandez, J. Romrell, E. Whidden, C. Jacobson, R. L. Rodriguez and M. S. Okun: Dual electrode thalamic deep brain stimulation for the treatment of posttraumatic and multiple sclerosis tremor. *Neurosurgery*, 58(4 Suppl 2), ONS-280-5; discussion ONS-285-6 (2006)

179. J. Herzog, W. Hamel, R. Wenzelburger, M. Potter, M. O. Pinsker, J. Bartussek, A. Morsnowski, F. Steigerwald, G. Deuschl and J. Volkmann: Kinematic analysis of thalamic versus subthalamic neurostimulation in postural and intention tremor. *Brain*, 130(Pt 6), 1608-25 (2007)

180. D. A. Lim, S. M. Khandhar, S. Heath, J. L. Ostrem, N. Ringel and P. Starr: Multiple target deep brain stimulation for multiple sclerosis related and poststroke Holmes' tremor. *Stereotact Funct Neurosurg*, 85(4), 144-9 (2007)

181. H. A. Wishart, D. W. Roberts, R. M. Roth, B. C. McDonald, D. J. Coffey, A. C. Mamourian, C. Hartley, L. A. Flashman, C. E. Fadul and A. J. Saykin: Chronic deep brain stimulation for the treatment of tremor in multiple sclerosis: review and case reports. *J Neurol Neurosurg Psychiatry*, 74(10), 1392-7 (2003)

182. H. S. Mayberg, A. M. Lozano, V. Voon, H. E. McNeely, D. Seminowicz, C. Hamani, J. M. Schwalb and S. H. Kennedy: Deep brain stimulation for treatment-resistant depression. *Neuron*, 45(5), 651-60 (2005)

183. B. Greenberg, Friehs, G., Carpenter, L., Tyrka, A., Malone, D., Rezai, A., Shapira, N., Foote, K., Okun, M., Goodman, W., Rasmussen, S., Price, L.: Deep Brain

Stimulation: Clinical Findings in Intractable Depression and OCD. *Neuropsychopharmacology*, 29, S32 (2005)

184. F. Jimenez, F. Velasco, R. Salin-Pascual, J. A. Hernandez, M. Velasco, J. L. Criales and H. Nicolini: A patient with a resistant major depression disorder treated with deep brain stimulation in the inferior thalamic peduncle. *Neurosurgery*, 57(3), 585-93; discussion 585-93 (2005)

185. N. Lipsman, J. S. Neimat and A. M. Lozano: Deep brain stimulation for treatment-refractory obsessive-compulsive disorder: the search for a valid target. *Neurosurgery*, 61(1), 1-11; discussion 11-3 (2007)

186. B. D. Greenberg, D. A. Malone, G. M. Friehs, A. R. Rezai, C. S. Kubu, P. F. Malloy, S. P. Salloway, M. S. Okun, W. K. Goodman and S. A. Rasmussen: Three-year outcomes in deep brain stimulation for highly resistant obsessive-compulsive disorder. *Neuropsychopharmacology*, 31(11), 2384-93 (2006)

187. L. Gabriels, P. Cosyns, B. Nuttin, H. Demeulemeester and J. Gybels: Deep brain stimulation for treatment-refractory obsessive-compulsive disorder: psychopathological and neuropsychological outcome in three cases. *Acta Psychiatr Scand*, 107(4), 275-82 (2003)

188. J. L. Abelson, G. C. Curtis, O. Sagher, R. C. Albucher, M. Harrigan, S. F. Taylor, B. Martis and B. Giordani: Deep brain stimulation for refractory obsessive-compulsive disorder. *Biol Psychiatry*, 57(5), 510-6 (2005)

189. B. Aouizerate, E. Cuny, C. Martin-Guehl, D. Guehl, H. Amieva, A. Benazzouz, C. Fabrigoule, M. Allard, A. Rougier, B. Bioulac, J. Tignol and P. Burbaud: Deep brain stimulation of the ventral caudate nucleus in the treatment of obsessive-compulsive disorder and major depression. Case report. *J Neurosurg*, 101(4), 682-6 (2004)

190. V. Sturm, D. Lenartz, A. Koulousakis, H. Treuer, K. Herholz, J. C. Klein and J. Klosterkotter: The nucleus accumbens: a target for deep brain stimulation in obsessive-compulsive- and anxiety-disorders. *J Chem Neuroanat*, 26(4), 293-9 (2003)

191. N. A. Shapira, M. S. Okun, D. Wint, K. D. Foote, J. A. Byars, D. Bowers, U. S. Springer, P. J. Lang, B. D. Greenberg, S. N. Haber and W. K. Goodman: Panic and fear induced by deep brain stimulation. *J Neurol Neurosurg Psychiatry*, 77(3), 410-2 (2006)

192. L. V. Laitinen: Emotional responses to subcortical electrical stimulation in psychiatric patients. *Clin Neurol Neurosurg*, 81(3), 148-57 (1979)

193. V. Visser-Vandewalle: DBS in tourette syndrome: rationale, current status and future prospects. *Acta Neurochir Suppl*, 97(Pt 2), 215-22 (2007)

194. L. Ackermans, Y. Temel, D. Cath, C. van der Linden, R. Bruggeman, M. Kleijer, P. Nederveen, K.

Schruers, H. Colle, M. A. Tijssen and V. Visser-Vandewalle: Deep brain stimulation in Tourette's syndrome: two targets? *Mov Disord*, 21(5), 709-13 (2006)

195. V. Visser-Vandewalle, Y. Temel, P. Boon, F. Vreeling, H. Colle, G. Hoogland, H. J. Groenewegen and C. van der Linden: Chronic bilateral thalamic stimulation: a new therapeutic approach in intractable Tourette's syndrome. Report of three cases. *J Neurosurg*, 99(6), 1094-100 (2003)

196. J. L. Houeto, C. Karachi, L. Mallet, B. Pillon, J. Yelnik, V. Mesnage, M. L. Welter, S. Navarro, A. Pelissolo, P. Damier, B. Pidoux, D. Dormont, P. Cornu and Y. Agid: Tourette's syndrome and deep brain stimulation. *J Neurol Neurosurg Psychiatry*, 76(7), 992-5 (2005)

197. N. J. Diederich, K. Kalteis, M. Stamenkovic, V. Pieri and F. Alesch: Efficient internal pallidal stimulation in Gilles de la Tourette's syndrome: a case report. *Mov Disord*, 20(11), 1496-9 (2005)

198. N. D. Schiff, J. T. Giacino, K. Kalmar, J. D. Victor, K. Baker, M. Gerber, B. Fritz, B. Eisenberg, J. O'Connor, E. J. Kobylarz, S. Farris, A. Machado, C. McCagg, F. Plum, J. J. Fins and A. R. Rezai: Behavioural improvements with thalamic stimulation after severe traumatic brain injury. *Nature*, 448(7153), 600-3 (2007)

199. T. Tsubokawa, T. Yamamoto, Y. Katayama, T. Hirayama, S. Maejima and T. Moriya: Deep-brain stimulation in a persistent vegetative state: follow-up results and criteria for selection of candidates. *Brain Inj*, 4(4), 315-27 (1990)

200. T. Yamamoto and Y. Katayama: Deep brain stimulation therapy for the vegetative state. *Neuropsychol Rehabil*, 15(3-4), 406-13 (2005)

201. T. Yamamoto, Y. Katayama, H. Oshima, C. Fukaya, T. Kawamata and T. Tsubokawa: Deep brain stimulation therapy for a persistent vegetative state. *Acta Neurochir Suppl*, 79, 79-82 (2002)

202. M. Leone: Chronic cluster headache: new and emerging treatment options. *Curr Pain Headache Rep*, 8(5), 347-52 (2004)

203. A. Franzini, C. Marras, P. Ferroli, O. Bugiani and G. Broggi: Stimulation of the posterior hypothalamus for medically intractable impulsive and violent behavior. *Stereotact Funct Neurosurg*, 83(2-3), 63-6 (2005)

204. R. G. Bittar, I. Kar-Purkayastha, S. L. Owen, R. E. Bear, A. Green, S. Wang and T. Z. Aziz: Deep brain stimulation for pain relief: a meta-analysis. *J Clin Neurosci*, 12(5), 515-9 (2005)

205. D. Tarsy, D. Apetauerova, P. Ryan and T. Norregaard: Adverse effects of subthalamic nucleus DBS in a patient with multiple system atrophy. *Neurology*, 61(2), 247-9 (2003)

206. M. O. Hebb, R. Garcia, P. Gaudet and I. M. Mendez: Bilateral stimulation of the globus pallidus internus to treat choreathetosis in Huntington's disease: technical case report. *Neurosurgery*, 58(2), E383; discussion E383 (2006)

207. L. Cif, B. Biolsi, S. Gavarini, A. Saux, S. G. Robles, C. Tancu, X. Vasques and P. Coubes: Antero-ventral internal pallidum stimulation improves behavioral disorders in Lesch-Nyhan disease. *Mov Disord*, 22(14), 2126-9 (2007)

208. G. Deuschl, J. Herzog, G. Kleiner-Fisman, C. Kubu, A. M. Lozano, K. E. Lyons, M. C. Rodriguez-Oroz, F. Tamma, A. I. Troster, J. L. Vitek, J. Volkmann and V. Voon: Deep brain stimulation: postoperative issues. *Mov Disord*, 21 Suppl 14, S219-37 (2006)

209. A. R. Rezai, B. H. Kopell, R. E. Gross, J. L. Vitek, A. D. Sharan, P. Limousin and A. L. Benabid: Deep brain stimulation for Parkinson's disease: surgical issues. *Mov Disord*, 21 Suppl 14, S197-218 (2006)

210. M. Emre, D. Aarsland, R. Brown, D. J. Burn, C. Duyckaerts, Y. Mizuno, G. A. Broe, J. Cummings, D. W. Dickson, S. Gauthier, J. Goldman, C. Goetz, A. Korczyn, A. Lees, R. Levy, I. Litvan, I. McKeith, W. Olanow, W. Poewe, N. Quinn, C. Sampaio, E. Tolosa and B. Dubois: Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Mov Disord*, 22(12), 1689-707 (2007)

211. T. D. Hälbig, D. Gruber, U. A. Kopp, P. Scherer, G. H. Schneider, T. Trottenberg, G. Arnold and A. Kupsch: Subthalamic stimulation differentially modulates declarative and nondeclarative memory. *Neuroreport*, 15(3), 539-43 (2004)

212. G. Koch, L. Brusa, C. Caltagirone, M. Oliveri, A. Peppe, P. Tiraboschi and P. Stanzione: Subthalamic deep brain stimulation improves time perception in Parkinson's disease. *Neuroreport*, 15(6), 1071-3 (2004)

213. U. Schroeder, A. Kuehler, A. Hennenlotter, B. Haslinger, V. M. Tronnier, M. Krause, R. Pfister, R. Sprengelmeyer, K. W. Lange and A. O. Ceballos-Baumann: Facial expression recognition and subthalamic nucleus stimulation. *J Neurol Neurosurg Psychiatry*, 75(4), 648-50 (2004)

214. U. Schroeder, A. Kuehler, K. W. Lange, B. Haslinger, V. M. Tronnier, M. Krause, R. Pfister, H. Boecker and A. O. Ceballos-Baumann: Subthalamic nucleus stimulation affects a frontotemporal network: a PET study. *Ann Neurol*, 54(4), 445-50 (2003)

215. K. Witt, F. Kopper, G. Deuschl and P. Krack: Subthalamic nucleus influences spatial orientation in extra-personal space. *Mov Disord*, 21(3), 354-61 (2006)

216. T. Stefurak, D. Mikulis, H. Mayberg, A. E. Lang, S. Hevenor, P. Pahapill, J. Saint-Cyr and A. Lozano: Deep brain stimulation for Parkinson's disease dissociates mood and motor circuits: a functional MRI case study. *Movement Disorders*, 18(12), 1508-16 (2003)

217. M. D. Phillips, K. B. Baker, M. J. Lowe, J. A. Tkach, S. E. Cooper, B. H. Kopell and A. R. Rezai: Parkinson disease: pattern of functional MR imaging activation during deep brain stimulation of subthalamic nucleus--initial experience. *Radiology*, 239(1), 209-16 (2006)

Send correspondence to: Alexander I. Troster, Department of Neurology, University of North Carolina School of Medicine at Chapel Hill, 3114 Bioinformatics Building (CB 7025),Chapel Hill, NC 27599-7025, U.S.A., Tel: 919-966-5549, Fax: 919-966-2922, E-mail: TrosterA@neurology.unc.edu