J Neurol (2003) 250 : 707–713
DOI 10.1007/s00415-003-1067-3

ORIGINAL COMMUNICATION

Thomas J. Loher
Klemens Gutbrod
Nina L. Fravi
Thomas Pohle
Jean-Marc Burgunder
Joachim K. Krauss

Thalamic stimulation for tremor

Subtle changes in episodic memory are related to stimulation per se and not to a microthalamotomy effect

Received: 10 September 2002
Received in revised form: 20 December 2002
Accepted: 15 January 2003

Dr. T. J. Loher · Dr. N. L. Fravi ·
Prof. Dr. J.-M. Burgunder
Department of Neurology
University of Berne
Inselspital
3010 Berne, Switzerland

PD Dr. K. Gutbrod
Section of Neuropsychological Rehabilitation
University of Berne
Inselspital
3010 Berne, Switzerland

Dr. T. Pohle
Department of Neurosurgery
University of Berne
Inselspital
3010 Berne, Switzerland

Prof. Dr. Joachim K. Krauss (✉)
Department of Neurosurgery
University Hospital, Klinikum Mannheim
Theodor-Kutzer-Ufer 1–3
68167 Mannheim, Germany
Tel.: +49-621/383-3142
Fax: +49-621/383-2004
E-Mail:
joachim.krauss@nch.ma.uni-heidelberg.de

Abstract The aim of this study was to investigate the impact of unilateral deep brain stimulation (DBS) of the ventrointermediate (Vim) thalamic nucleus on neuropsychological functioning comparing stimulation-on with stimulation-off conditions. Nine patients [five patients with Parkinson's Disease (PD), two patients with essential tremor (ET) and 2 patients with multiple sclerosis (MS)] underwent comprehensive neuropsychological testing for cognitive functions, including general mental impairment, aphasia, agnosia, executive and constructional abilities, learning, memory, cognitive processing speed and attention as well as depression. The neuropsychological assessments were performed at least 6 months postoperatively (mean 9 months). Testing in the stimulation-on and stimulation-off condition was obtained within a period of 3 to 4 weeks. Unilateral DBS resulted in improvement of tremor in all patients. There were no significant differences between the stimulation-on and the stimulation-off condition with the exception of a decrement of word-recall in the short delay free-recall subtest of the Rey Auditory-Verbal Learning Test (RAVLT). Subgroup analysis indicated that the impairment in word-recall was related to left-sided thalamic stimulation. Our study confirms that chronic unilateral DBS is a safe method with regard to cognitive function. The subtle changes in episodic memory are related to stimulation per se and not to a microthalamotomy effect.

Key words deep brain stimulation · thalamus · neuropsychology · Parkinson's disease · tremor

Introduction

Functional stereotactic surgery is now well established for treatment of medically intractable tremor in Parkinson's disease (PD) and essential tremor (ET) [1, 2]. Thalamic deep brain stimulation (DBS) nowadays is considered an accepted alternative to radiofrequency lesioning given its reversibility and the option to optimize stimulation settings [3–9]. Long-term control of tremor is achieved both in PD and in ET [1, 10, 11]. Only a few studies have investigated neurobehavioral functioning in patients with thalamic DBS [1, 12–16]. In general, only subtle changes of cognition were reported. Postoperative assessments were usually performed under stimulation-on conditions leaving the question open whether these changes were secondary to a microthalamotomy effect or whether they were related to stimulation per se. To our knowledge, only two case reports were published investigating this issue, yielding inconsistent results with regard to the direct effects of stimulation on language and memory [15, 16]. Thus, the present study was

designed to evaluate neurobehavioral functioning in a larger sample of patients with chronic thalamic DBS while on and while off stimulation at least 6 months after surgery.

Patients and methods

Patients

Nine patients who achieved successful control of their medically refractory tremor after unilateral chronic thalamic ventrointermediate (Vim) DBS were included in the present study. Patients gave their informed consent prior to their inclusion in the study. In all patients, tremor had been the predominant symptom. There were five men and four women. Their mean age at surgery was 71.4 years (range 48–81). Tremor was related to PD in five patients, to ET in two patients, and to multiple sclerosis (MS) in two patients. All patients were right-handed for writing. No patient had undergone thalamotomy or other neurosurgical procedures before. Implantation was performed on the left side in six patients and on the right side in the three others.

Neurosurgical procedure

Principles and techniques of the surgical procedure have been described in detail elsewhere [7, 17, 18]. In brief, the two successive steps of the procedure were performed in the same operative session. First, a quadripolar DBS electrode (3387, Medtronic Inc., Minneapolis, MN) was implanted into the Vim nucleus under CT-stereotactic guidance under local anesthesia. The tentative target in the Vim was determined at 12–14 mm lateral to the midline, 3–4 mm behind the midcommissural point, and 1 mm below the intercommissural line. Thresholds for both arrest of tremor and evoked motor and sensory responses were examined to further refine the target. In a second step, the implantable pulse generator (IPG; Itrel II, Medtronic Inc., Minneapolis, MN) was placed in a subcutaneous pouch below the clavicle under general anesthesia. Postoperatively, all patients had 1 mm axial CT to rule out hemorrhage and to confirm correct placement of the electrodes. The first programming of the IPG was done within 24 hours after the operation, and stimulation settings were adjusted on follow-up visits to achieve optimal tremor control.

Clinical evaluation

All patients were included in a prospective study protocol and underwent standardized clinical evaluations pre- and postoperatively [7]. Motor evaluations included the Unified Parkinson's Disease Rating Scale (UPDRS) and a modified tremor scale on and off medication [19, 20]. In order to allow comparison of patients with different tremors, global improvement of tremor was rated as excellent (> 90 % improvement), marked (70–90 %), moderate (30–70 %) and minor/poor (0–30 % improvement, unchanged or worse).

Neuropsychological evaluations at a mean of 9 months after surgery (range 6–13) were performed during two separate visits within 3–4 weeks (mean, 3.7) while the IPGs were either on or off. Five patients first underwent the stimulation-on testing, whereas the other four patients first had the stimulation-off tests. Patients were tested after having taken their usual medication, i. e. in the on-medication condition in PD patients.

Neuropsychological assessment

A comprehensive neuropsychological test battery was administered. With respect to the mean age of the study sample, the tests used were primarily selected on the basis [1] that normative data for elderly healthy subjects were available, and [2] that the test battery should not take longer than 1 hour. Most of the tests were adapted from „The Consortium to Establish a Registry for Alzheimer's Disease" (CERAD) neuropsychological test battery [21] in the Swiss-German adaptation of Thalmann [22]. The majority of the tests used were selected to measure six aspects of neuropsychological function, as summarized below. For a more detailed description and further references of the tests used in this study, see Morris [21] and Spreen and Strauss [23].

The neuropsychological examination was administered by a neuropsychologist (K. G.) who was blinded with regard to whether the stimulator was on or off. Form A of the RAVLT was always administered in session 1, form B always in session 2. Because all other tests used have only one version, the same tests were repeated in the stimulation-on and stimulation-off examination.

Screening for general mental impairment, aphasia and agnosia

To screen for general mental impairment the Mini-Mental State Examination (MMSE) was used. Tests used to screen for aphasia and agnosia included the modified Boston Naming Test of the CERAD and the Agnosia Screening Task of Schnider [24]. The MMSE is a well known brief general cognitive battery that measures orientation, immediate and delayed memory, concentration, language, and praxis [25]. In the Boston Naming Test subjects are asked to name 15 object drawings. In the Agnosia Screening Task, 11 items of overlapping figures, silhouettes and incomplete drawings or letters are presented to patients for recognition.

Executive Abilities

Tests utilized to measure executive functions included the Stroop Test [26, 27], the Verbal fluency Task of the CERAD and a Go/nogo Test of the Test Battery for Assessing Attentional Disorders (TAP) of Zimmermann and Fimm [28]. All these tests are sensitive to frontal lobe disorders. The Stroop Test consists of three parts. In part I, patients must name as quickly as possible the color of 24 dots printed in blue, green, red or yellow. Part II is similar to part I, except that the dots are replaced by common words ("when", "hard", "over"). The patients are required to name the colors in which the stimuli are printed, and disregard their verbal content. Part III is similar to part I and II, but here the colored stimuli are the color names "blue", "green", "red", "yellow", so that the print color never corresponds to the color name. In the Verbal Fluency Task patients are asked to produce orally as many animal names as possible in one minute. In the Go/nogo Test of the TAP one of two stimuli (a cross or an oblique cross) are presented on a computer screen, one of which is critical and has to be responded by pressing a key.

Constructional Abilities

To test constructional abilities the subtest Constructional Praxis of the CERAD was administered. In this test, four line drawings of figures of increasing complexity (a circle, a diamond, two intersecting rectangles, and a cube) are presented to the patients for copying.

Learning and Memory

Tests to assess learning and memory included the Rey Auditory-Verbal Learning Test (RAVLT) and the subtest Recall of Constructional Praxis of the CERAD [23]. In the RAVLT, 15 nouns (List A) are read aloud for five consecutive trials (trials A1-A5) to patients, each trial followed by a free-recall test. Upon completion of trial A5, an interference list of 15 words (list B) is presented, followed by a free-recall test on that list. Immediately following this, again recall of the first list (short delay free-recall) is tested without further presentation of those words (trial A6). After a 20-minute delay period (long delay free-recall) each patient is again required to recall words from list A

(trial A7). Finally, recognition is tested where the patient must identify list A words from a list of 50 words containing all items from list A and B and 20 words semantically similar to those in lists A and B. For this study two alternate forms (form A and B) similar to that published in Spreen and Strauss were used [23]. In the subtest Recall of Constructional Praxis, delayed-recall for the four line drawings of Constructional Praxis is tested.

Cognitive Processing Speed and Attention

To test cognitive processing speed and attention, the subtest Alertness of the TAP was used. This test includes a simple and cued reaction time task (pressing a key) with a visual test stimulus and an acoustic cue. The test consists of 4 trials with 20 presentations each in an ABBA-design (A = without cue; B = with cue). The simple reaction time has been shown to be a valid measure of phasical alertness [28].

Depression

To screen for depression, patients were given the Beck Depression Inventory (BDI) [29]. In this test the patient checks 21 four-choice self-report statements for the choice most appropriate to him or her. The statements refer to areas like sadness, guilt, suicidal ideation, insomnia etc.

Statistical analysis

Descriptive statistics were calculated using SPSS for Windows software. Due to the sample size non-parametric Wilcoxon tests were computed to compare stimulation-on and stimulation-off scores [30]. Separate statistical analyses were performed for the total group of patients (n = 9), and for subgroups according to the side of stimulation. To test, whether one of the two subgroups were more severely disturbed, separate Mann-Whitney-U-Tests were performed. A P-value of < 0.05 was considered to indicate statistical significance.

Results

Operative morbidity and symptomatic outcome

There were no intraoperative complications. Postoperatively, one patient had a seizure and subsequently a mild hemiparesis on the right side which was completely resolved within 3 weeks postoperatively. At the postoperative assessment under stimulation-on conditions all patients had useful improvement of their tremors. The improvement was classified as excellent in five patients, marked in two patients and moderate in two other patients. PD patients presented with a significant improvement in the UPDRS subscores for contralateral tremor. More details on outcome have been published elsewhere [7].

Neurobehavioral functioning in the stimulation-off and the stimulation-on condition

The patients' mean scores during stimulation-off and stimulation-on conditions as compared with normative data of elderly subjects are shown in Table 1. Patients had impairments in frontal lobe tests, constructional praxis and cognitive processing speed which were below two standard deviations of the means of the normative data (age 70 +). This was evident both for the stimulation-on scores and for the stimulation-off scores. There was only one significant difference when the stimulation-on condition was compared with the stimulation-off condition. In the stimulation-off examination patients could significantly recall more words in the short delay free-recall condition of the RAVLT (M = 5.3) than in the stimulation-on (= 3.4) examination ($p = 0.04$). A trend was also found for the long delay free-recall condition of the RAVLT which, however, did not reach statistical significance. Patients in the stimulation-off examination (M = 4.0) recalled more words than in the stimulation-on (M = 2.8) examination ($p = 0.08$). All other statistical tests were non-significant. The subgroup analyses of patients with stimulation either on the left side or right side (Table 2) revealed that the observed difference in the short delay free-recall condition was related to left-sided stimulation. Furthermore, altered simple reaction times during stimulation were found in patients with left-sided stimulation. In the right-sided stimulation group none of the comparisons reached statistical significance. These results were not due to the fact that the left-sided stimulation group was generally more severely disturbed than the right group, since all statistical comparisons between the groups (Mann-Whitney-U-Tests) in the stimulation-off examination were non-significant.

Discussion

Thalamic DBS in tremor patients is associated with only mild changes in neurobehavioral functioning. Our evaluation is the first study on a group of tremor patients undergoing Vim thalamic DBS that differentiates neurobehavioral functioning with and without stimulation during chronic DBS. The most remarkable finding was a significant deterioration on the short delay free-recall of a verbal memory test (RAVLT) when the stimulator was on. This subtle change in episodic memory is a stimulation effect per se and shows that Vim DBS may have a mild impact on memory performance. It is associated with left-sided, but not with right-sided stimulation. One limitation of the present study is the relatively small number of patients. It would be useful to confirm the present findings, in particular with regard to lateralisation of the effect in a larger and more homogeneous group of patients. Further evaluations could also include comparison of preoperative assessments with the stimulation-off condition.

The distinct impairment in frontal lobe tests, constructional praxis and cognitive processing speed in our patients were observed both under stimulation-on and stimulation-off conditions. These deficits were most evident in the PD patients subgroup. Such deficits in ad-

Table 1 Normative data (age 70 +) and mean performance levels (+ SD) of the 9 patients who underwent unilateral Vim DBS

Function/Test[a]	Normative-Data Mean (SD)	Stimulation-on Mean (SD)	Stimulation-off Mean (SD)	Statistics[b] p
General mental impairment, aphasia and agnosia				
• Mini Mental State (max. 30)	28.9 (1.2)	27.2 (2.5)	26.5 (1.7)	0.38
• Boston Naming Test (max. 15)	14.0 (1.1)	12.6 (0.7)	12.8 (1.4)	0.44
• Agnosia Screening Task (max. 11)	n. a.[c]	10.0 (1.3)	10.0 (2.0)	1.00
Executive Abilities				
• Stroop Test (part III)				
– Time (s.)	39.6 (13.3)	51.0 (21.5)	61.6 (20.7)	0.12
– Errors	0.75 (1.15)	3.7[d] (4.1)	3.9[d] (4.1)	0.83
• Word Fluency	21.3 (5.5)	10.3[d] (3.3)	9.7[d] (2.8)	0.39
• Go/nogo				
– Time (ms.)	387 (76)	424 (111)	435 (112)	0.87
– Errors	2.0 (0.5)	4.8[d] (4.9)	3.0[d] (3.3)	0.10
Constructional Abilities				
• Constructional Praxis (max. 11)	10.4 (0.9)	6.4[d] (3.8)	4.7[d] (3.9)	0.17
Learning and Memory				
• Rey Auditory-Verbal Learning Test[e]				
– Total List A	32.6 (8.3)	27.9 (6.5)	29.1 (5.1)	0.29
– Short Delay Free Recall (Trial A6)	6.4 (1.7)	3.4 (3.2)	5.3 (2.1)	0.04
– Long Delay Free Recall (Trial A7)	5.6 (2.6)	2.8 (3.1)	4.0 (3.1)	0.08
– Recognition	11.5 (2.6)	12.3 (1.7)	12.2 (2.4)	0.89
• Delayed Recall of Constructional Praxis	8.9 (2.2)	4.6[d] (2.7)	4.7[d] (3.1)	0.89
Processing Speed and Attention				
• Alertness				
– without cue (ms.)	233 (39)	349[d] (180)	416[d] (153)	0.13
– with cue (ms.)	219 (38)	294[d] (138)	369[d] (168)	0.50
– Phasic Alertness	0.05 (0.25)	0.12 (0.31)	0.12 (0.19)	1.00
Depression				
• Beck Depression Inventory	6.5 (5.2)	6.2 (3.9)	5.6 (4.9)	0.62

[a] For description of tests and normative data see *Neuropsychological Assessment*; [b] Wilcoxon Tests (stimulation-on and stimulation-off scores compared); [c] Normative data not available; [d] Below 2 SDs of the mean of normative data; [e] Normative data for men, age 70 + (Table 10–17 from Spreen and Strauss [24])

vanced PD are well known, especially in frontal lobe tests, and are due to dysfunction of frontal-subcortical circuits [31–34].

The results of our study that thalamic DBS has only little impact on overall cognitive functioning are generally in line with previous studies that compared patients' performance prior to surgery and postoperatively during stimulation-on [1, 12–16]. Data on the effects of stimulation on language and memory function, however, are conflicting. In a series of 40 patients with ET Tröster and colleagues reported statistically significant amelioration of delayed word list recognition, and prose recall 3 months after surgery [13]. The only significant impairment they found was a deterioration on a verbal fluency test. In a more recent study of nine PD patients undergoing unilateral Vim DBS Woods and colleagues found significant improvements in immediate memory for prose, delayed word list recall, and conceptualisation 1 year after surgery [14]. Regarding verbal fluency, three studies showed postoperative deterioration [1, 12, 13], while other studies reported improvements [14–16].

The impairment of immediate recall during stimulation found in our study is in accordance with the change in verbal memory function referred in a case report of a PD patient undergoing neuropsychological testing under comparable conditions. In this case, improvement of semantic verbal fluency and visual confrontation naming was found, but stimulation interfered with immediate verbal list recall [15]. Based on these observations the authors hypothesized that thalamic stimulation focuses attention on the external environment while blocking activation of internalised information. Neuropsychological testing in another case study of a patient with bilateral Vim DBS for ET reported an improvement in delayed word list recall with stimulation compared with when the stimulators were turned off [16]. The authors speculated that bilateral Vim DBS somehow might facilitate verbal retrieval processes.

The effect we have observed regarding laterality of stimulation is in accordance with laterality-specific changes reported earlier [1, 13]. Benabid and colleagues found a slightly lateralized decrease in performance fluency, especially affecting verbal performance, when the left Vim nucleus was stimulated, and affecting spatial

Table 2 Mean performance levels (+ SD) in the two subgroups of patients with unilateral Vim DBS on the left or right side

Function/Test[a]	Stimulation on the left side (n = 6)			Stimulation on the right side (n = 3)		
	On Mean (SD)	Off Mean (SD)	Statistics[b] p	On Mean (SD)	Off Mean (SD)	Statistics[b] p
General mental impairment, aphasia and agnosia						
• Mini Mental State (max. 30)	26.3 (2.4)	26.1 (1.8)	0.70	29.0 (1.7)	27.0 (1.7)	0.11
• Boston Naming Test (max. 15)	12.5 (0.8)	13.0 (1.4)	0.40	12.7 (1.7)	12.7 (1.5)	1.00
• Agnosia Screening Task (max. 11)	10.0 (1.5)	9.6 (2.4)	0.41	10.0 (1.0)	10.7 (0.6)	0.32
Executive Abilities						
• Stroop Test (part III)						
– Time (s.)	52.2 (23.6)	65.5 (24.8)	0.14	48.7 (21.1)	53.7 (6.1)	0.60
– Errors	2.2 (0.9)	3.8 (2.8)	0.14	6.7 (6.6)	4.0 (6.9)	0.11
• Word Fluency	10.0 (4.0)	9.8 (2.3)	0.89	11.0 (1.0)	9.3 (2.3)	0.18
• Go/nogo						
– Time (ms.)	426 (57)	475 (117)	0.50	700 (126)	547 (109)	0.18
– Errors	6.0 (5.3)	3.6 (3.7)	0.13	1.6 (2.0)	1.5 (0.7)	0.66
Constructional Abilities						
• Constructional Praxis (max. 11)	5.7 (4.5)	3.5 (4.0)	0.28	8.0 (1.0)	7.0 (2.6)	0.42
Learning and Memory						
• Rey Auditory-Verbal Learning Test						
– Total List A	26.0 (2.0)	27.5 (6.5)	0.28	31.6 (11.1)	32.3 (7.4)	0.78
– Short Delay Free Recall (Trial A6)	2.1 (2.3)	4.5 (3.2)	0.05	6.0 (3.6)	7.0 (1.7)	0.42
– Long Delay Free Recall (Trial A7)	1.7 (2.9)	3.0 (3.1)	0.09	5.0 (2.6)	6.0 (2.6)	0.09
– Recognition	12.2 (2.0)	12.2 (1.7)	0.91	12.7 (0.6)	12.3 (1.5)	0.66
• Delayed Recall of Constructional Praxis	4.8 (2.6)	6.3 (3.1)	0.18	4.0 (3.0)	3.0 (2.6)	0.42
Processing Speed and Attention						
• Alertness						
– without cue (ms.)	312 (78)	435 (173)	0.04	556 (189)	507 (113)	0.16
– with cue (ms.)	280 (105)	413 (192)	0.23	479 (98)	398 (146)	0.18
– Phasic Alertness	0.09 (0.36)	0.06 (0.17)	0.68	0.12 (0.15)	0.27 (0.17)	0.66
Depression						
• Beck Depression Inventory	4.8 (3.5)	3.6 (3.4)	0.62	9.0 (3.6)	9.6 (5.5)	0.79

[a] For description of tests see Neuropsychological Assessment; [b] Wilcoxon Tests (stimulation-on and stimulation-off scores compared)

performance, when stimulation was on the right side [1]. Laterality-specific changes in language and memory have also been demonstrated during intraoperative stimulation studies when performing thalamotomies. Ojemann noted that stimulation of the ventrolateral (VL) thalamus affected speech mechanisms in 9 out of 45 patients [35]. This effect was observed, however, only on the left side. Ojemann's group also demonstrated that intraoperative VL thalamic stimulation on the left but not on the right side significantly affected verbal memory [35–37]. Recently, Wester and Hugdahl confirmed these observations [38, 39].

The anatomical coordinates which we have used for the Vim are in agreement with the topography of the Vim as depicted in the axial cuts in the Schaltenbrand-Wahren stereotactic atlas [40]. According to the coronal and sagittal Schaltenbrand-Wahren cuts they approximate to the so-called Vim-Vop border zone. We did not intend to target the Vop (ventrooralis posterior). There has been some controversy regarding the subdivision of the ventrolateral thalamus into the ventrooralis anterior and the ventrooralis posterior. Jones, recently, claimed that Hassler's Vop is a "factitious construct" [41]. According to the nomenclature elaborated by Jones "the region identified as Vop by Hassler is clearly the region in which islands and fingers of cells proper to VLa (Voa) and VLp (Vim) interdigitate". Jones also states that "Vop has no standing as an independent nucleus and an equivalent name in monkey and human is not called for".

Since the functional effects of DBS on neuronal substrates are still poorly understood, one can only speculate on the mechanisms underlying the effect of thalamic DBS on cognitive functioning [1, 42]. In view of the concept of segregation and parallel processing of multiple motor and nonmotor loops in the corticobasal ganglionic-thalamic-cortical circuitry, cognitive changes may be due to unspecific stimulation of nonmotor circuits. In accordance with this hypothesis, Ceballos-Bauman and colleagues showed in a recent PET study on 6 patients undergoing left-sided chronic Vim DBS for ET that there is, apart from regional cerebral blood flow (rCBF) changes in motor areas, also activation of nonmotor areas, such as the cingulate area and the gyrus frontalis inferior [43]. Furthermore, electrophysiological studies suggest direct involvement of the thalamus in

verbal memory processes. Extracellular microelectrode recording investigations have shown specific responses of neuronal subpopulations in the thalamic Vop and in the zona incerta during intraoperative memory testings [44].

Thalamic surgery leads to effective long-term control of tremor both in PD and in ET patients [1, 7, 9, 10, 11]. Regarding the limited effect of thalamic surgery on rigidity and bradykinesia in PD, as compared with pallidal and STN surgery, there has been a substantial reduction of thalamic surgery in PD in the past few years. It is anticipated that even fewer PD patients will undergo thalamic surgery in the future [45]. Thalamic Vim stimulation, however, will remain an important therapeutic option for ET and for other patients with medically-intractable tremors.

In conclusion, our data show that Vim DBS is a relatively safe treatment from a neuropsychological standpoint. The significant but subtle change in episodic memory is due to stimulation per se and not a microthalamotomy effect.

Disclosure Joachim K. Krauss is a consultant to Medtronic, Inc.

References

1. Benabid AL, Pollak P, Gao D, Hoffmann D, Limousin P, Gay E, Payen I, Benazzouz A (1996) Chronic electrical stimulation of the ventralis intermedius nucleus of the thalamus as a treatment of movement disorders. J Neurosurg 84:203–214
2. Hallet M, Litvan I (2000) Scientific Position Paper of the Movement Disorder Society. Evaluation of Surgery for Parkinson's Disease. Task Force on Surgery for Parkinson's Disease of the American Academy of Neurology Therapeutic and Technology Assessment Committee. Mov Disord 15: 436–438
3. Koller W, Pahwa R, Busenbark K, Hubble J, Wilkinson S, Lang A, Tuite P, Sime E, Lozano A, Hauser R, Malapira T, Smith D, Tarsy D, Miyawaki E, Norregaard T, Kormos T, Olanow CW (1997) High-frequency unilateral thalamic stimulation in the treatment of essential and parkinsonian tremor. Ann Neurol 42:292–299
4. Limousin P. Speelman JD, Gielen F, Janssens M, study collaborators (1999) Multicentre European study of thalamic stimulation in parkinsonian and essential tremor. J Neurol Neurosurg Psychiatry 66:289–296
5. Koller WC, Pahwa R, Lyons KE, Wilkinson SB (2000) Deep brain stimulation of the Vim nucleus of the thalamus for the treatment of tremor. Neurology 55(Suppl. 6):29–33
6. Schuurman PR, Bosch DA, Bossuyt PMM, Bonsel GJ, van Someren EJW, de Bie RMA, Merkus MB, Speelman JD (2000) A comparison of continuous thalamic stimulation and thalamotomy for suppression of severe tremor. N Engl J Med 342:461–468
7. Krauss JK, Simpson RK, Ondo WG, Pohle T, Burgunder JM, Jankovic J (2001) Concepts and methods in chronic thalamic stimulation for treatment of tremor: technique and application. Neurosurgery 48:535–543
8. Obwegeser AA, Uitti RJ, Witte RJ, Lucas JA, Turk MF, Wharen RE (2001) Quantitative and qualitative outcome measures after thalamic deep brain stimulation to treat disabling tremors. Neurosurgery 48:274–284
9. Ondo W, Almaguer M, Jankovic J, Simpson RK (2001) Thalamic deep brain stimulation: comparison between unilateral and bilateral placement. Arch Neurol 58:218–222
10. Koller WC, Lyons KE, Wilkinson SB, Troster AI, Pahwa R (2001) Long-term safety and efficacy of unilateral deep brain stimulation of the thalamus in essential tremor. Mov Disord 16: 464–468
11. Lyons KE, Koller WC, Wilkinson SB, Pahwa R (2001) Long term safety and efficacy of unilateral deep brain stimulation of the thalamus for parkinsonian tremor. J Neurol Neurosurg Psychiatry 71:682–684
12. Caparros-Levebvre D, Blond S, Pecheux N, Pasquier F, Petit H (1992) Evaluation neuropsychologique avant et après stimulation thalamique chez 9 parkinsoniens. Rev Neurol (Paris) 148: 117–122
13. Tröster AI, Fields JA, Pahwa R, Wilkinson SB, Straits-Tröster KA, Lyons K, Kieltyka J, Koller WC (1999) Neuropsychological and quality of life outcome after thalamic stimulation for essential tremor. Neurology 53:1774–1780
14. Woods SP, Fields JA, Lyons KE, Koller WC, Wilkinson SB, Pahwa R, Tröster AI (2001) Neuropsychological and quality of life changes following unilateral thalamic deep brain stimulation in Parkinson's disease: a one-year follow-up. Acta Neurochir (Wien) 143: 1273–1278
15. Tröster AI, Wilkinson SB, Fields JA, Miyawaki K, Koller WC (1998) Chronic electrical stimulation of the left ventrointermediate (Vim) thalamic nucleus for the treatment of pharmacotherapy-resistant Parkinson's disease: a differential impact on access to semantic and episodic memory? Brain Cogn 38:125–149
16. Lucas JA, Rippeth JD, Uitti RJ, Shuster EA, Wharen RE (2000) Neuropsychological functioning in a patient with essential tremor with and without bilateral VIM stimulation. Brain Cogn 42:253–267
17. Krauss JK, King DE, Grossman RG (1998) Alignment correction algorithm for transformation of stereotactic anterior commissure/posterior commissure-based coordinates into frame coordinates for image-guided functional neurosurgery. Neurosurgery 42: 806–811
18. Krauss JK, Grossman RG (2001) Principles and techniques of movement disorder surgery. In: Krauss JK, Jankovic J, Grossman RG (eds) Surgery for Parkinson's disease and movement disorders. Lippincott Williams & Wilkins, Philadelphia, pp 74–109
19. Fahn S, Elton RL, members of the UPDRS Development Committee (1987) Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Goldstein M, Calne DB (eds) Recent development in Parkinson's disease, vol. 2. Macmillan, Florham Park, NJ, pp 153–163
20. Fahn S, Tolosa E, Marin C (1988) Clinical rating scale for tremor. In: Jankovic J, Tolosa E (eds) Parkinson's Disease and Movement Disorders. Urban and Schwarzenberg, Munich, pp 225–234

21. Morris JC, Heyman A, Mohs RC, Hughes JP, van Belle G, Fillenbaum G, Mellits ED, Clark C (1989) The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. Neurology 39:1159–1165
22. Thalmann B, Monsch AU, Schneitter M, et al. (1998) CERAD-neuropsychological battery – A minimal data set to be used as a common assessment tool for dementia. Neurobiol Aging 19: 4S:33
23. Spreen O, Strauss E (1998) A compendium of neuropsychological tests. Oxford University Press, New York
24. Schnider A (1997) Verhaltensneurologie. Georg Thieme, Stuttgart, pp 82–99
25. Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiat Res 12:189–198
26. Perret E (1974) The left frontal lobe of man and the suppression of habitual responses in verbal categorical behavior. Neuropsychologia 12:323–330
27. Regard M, Strauss E, Knapp P (1982) Children's production of verbal and nonverbal fluency. Percept Mot Skills 55:839–844
28. Zimmermann P, North P, Fimm B (1993) Diagnosis of attentional deficits: theoretical considerations and presentation of a test battery. In: Stachowiak FJ (ed) Developments in the assessment and rehabilitation of brain-damaged patients. Gunter Narr Verlag, Tübingen, pp 3–17
29. Hautzinger M, Bailer M, Worall H, Keller F (1994) Depressions-Inventar (BDI). Verlag Hans Huber, Bern
30. Markowitsch HJ and Pritzel M (1977) Nonparametric statistics for the analysis of behavior-related single unit data. Physiol Behav 18:717–719
31. Taylor AE, Saint-Cyr JA, Lang AE (1986) Frontal lobe dysfunction in Parkinson's disease: the cortical focus of neostriatal outflow. Brain 109: 845–883
32. Brown RG, Marsden CD (1990) Cognitive function in Parkinson's disease: from description to theory. Trends Neurosci 13:21–29
33. Dubois B, Pillon B (1997) Cognitive deficits in Parkinson's disease. J Neurol 244:2–8
34. Tröster AI, Fields JA, Koller WC (2000) Parkinson's disease and parkinsonism. In: Coffey CE, Cummings JL (eds) American Psychiatric Press textbook of geriatric neuropsychiatry 2nd ed. American Psychiatric Press, Washington, DC
35. Ojemann GA (1977) Asymmetric function of the thalamus in man. Ann N Y Acad Sci 299:380–396
36. Ojemann GA, Hoyenga KB, Ward AA jr (1971) Prediction of short-term verbal memory disturbance after ventrolateral thalamotomy. J Neurosurg 35: 203–210
37. Ojemann GA (1985) Enhancement of memory with human ventrolateral thalamic stimulation: Effect evident on a dichotic listening task. Appl Neurophysiol 48:212–215
38. Wester K, Hugdahl K (1997) Thalamotomy and thalamic stimulation: effects on cognition. Stereotact Funct Neurosurg 69:80–85
39. Hugdahl K, Wester K (1997) Lateralized thalamic stimulation: effects on verbal memory. Neuropsychiatry Neuropsychol Behav Neurol 10:155–161
40. Schaltenbrand G, Wahren P (1977) Atlas for stereotaxy of the human brain. Stuttgart, Thieme
41. Jones EG (2001) Morphology, nomenclature and connections of the thalamus and basal ganglia. In: Krauss JK, Jankovic J, Grossman RG (eds) Surgery for Parkinson's disease and movement disorders. Lippincott Williams & Wilkins, Philadelphia, pp 24–47
42. Benabid AL, Pollak P, Hoffman D, Limousin P, Gao DM, LeBas JF, Benazzouz A, Segebarth C, Grand S (1998) Chronic stimulation for Parkinson's disease and other movement disorders. In: Gildenberg PL, Tasker RR (eds) Textbook of stereotactic and functional neurosurgery. McGraw-Hill, New York, pp 1199–1212
43. Ceballos-Baumann AO, Boecker H, Fogel W, Alesch F, Bartenstein P, Conrad B, Diederich N, von Falkenhayn I, Moringlane JR, Schwaiger M, Tronnier VM (2001) Thalamic stimulation for essential tremor activates motor and deactivates vestibular cortex. Neurology 56: 1347–1354
44. Gogolitsin YL, Nechaev VB (1993) Thalamic neuronal populations responding to selectively remembered words. Stereotact Funct Neurosurg 60: 147–151
45. Obeso JA, Guridi J, Rodriguez-Oroz MC, Alvarez L, Macias R (2001) Role of surgery in the management of Parkinson's disease. In: Krauss JK, Jankovic J, Grossman RG (eds) Surgery for Parkinson's disease and movement disorders. Lippincott Williams & Wilkins, Philadelphia, pp 135–143