

Deep Brain Stimulation for the Treatment of Movement Disorders

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Recently, deep brain stimulation (DBS) has been applied in many patients to treat movement disorder. Though this new methodology is in the stage of settlement, many aspects on DBS has not been well known yet. I reviewed related articles and my experience to summarize facts on DBS.

KEY WORDS : Deep brain stimulation · Movement disorder.

Introduction

Pain relief through electrical stimulation of anatomic sites was first reported in 1954 and 1956 as a “side aspect” observed during psychosurgery^{62,109}. In 1962, Mazars and colleagues investigated the treatment of deafferentation pain with intermittent electrical stimulation inside the sensory thalamic ventroposterolateral nucleus (VPL)⁹³.

Unexpectedly, beside pain they could also control associated abnormal movements. However, their efforts to treat patients with primary movement disorders using the same target failed. From 1972-1975, Bechtereva and coworkers published several articles dealing with therapeutic deep brain stimulation in patients with movement disorders¹⁵⁻¹⁷. To treat one patient suffering from Wilson’s disease, one from torsion dystonia and a third from Parkinson’s disease (PD), they stereotactically implanted bundles of electrodes each bundle containing 24-40 wires into the individual target area. Stimulation was performed in intervals, two or three times a week. Munding, who worked in Freiburg, Germany, started in 1975 with the stimulation of deep brain structures (ventrolateral (VL) thalamus) for the treatment of movement disorders⁹⁹ and in 1982, he reported about five successfully treated cases¹⁰⁰. Cooper and associates evaluated the VL-thalamus close to the internal capsule (stimulation with 70 Hz). Promising results were reported for patients with cerebral palsy³⁷.

Another innovative approach was described in 1980 by Brice and McLellan. These authors stimulated continuously with 75-150 Hz in the region below the thalamus and were able to suppress intention tremor in three female patients with multiple sclerosis³⁰.

In 1987, Benabid and coworkers reported the first series containing selected tremor patients, whose symptoms were significantly alleviated after stimulation inside the ventrointermedius (Vim) thalamic nucleus²⁰. Other keystones have been the treatment of both motor symptoms of Parkinson’s disease (PD) and L-Dopa induced dyskinesias with high-frequency stimulation inside the internal segment of the globus pallidus (GPi)¹²⁶ or the subthalamic nucleus (STN)^{22,85}, and the evaluation of pallidal stimulation for the treatment of dystonia^{38,75,80}.

Mainly the unequivocally lower rate of severe permanent adverse events if compared to lesioning, the reversibility of stimulation induced side effects, and the option to adopt the need of stimulation energy on the course of a progressive disease like Parkinson’s disease (PD) favored during the last 10 years increasingly the use DBS instead of ablative surgery.

The here presented review will give an introduction into pathophysiological considerations, which underlay those diseases treated with DBS, and its implications for the choice of the appropriate target. Other theoretical issues will address assumptions related to the action of DBS, and some details of the technical equipment. The clinical results are mainly focused on practical details to supply the reader with information useful for the daily routine. The comparably extended list of references might serve for those who would like to go deeper into this topic.

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Technical Considerations

The development of battery-powered cardiac pacemakers was basically the background for modern, totally implantable neural stimulators. Brain electrodes of the only commercially available system are made of platinum and iridium and are insulated by ethylene. For insertion they contain a centrally stabilizing but removable stylet. Mostly versions with four linearly arranged contacts are used (length of one contact: 1.5mm, outer diameter: approx. 1.3mm.). Two types of these quadripolar electrodes are available: one with reduced space between contacts (0.5mm, model 3389, Medtronic, MA, USA) and one with longer distances (1.5mm, model 3387, Medtronic, MA, USA). Electrode type 3387 is used for stimulation inside motor thalamus or pallidum, the version with reduced space is implanted for DBS inside the STN. The stimulation electrodes are either connected to an externalized cable for test stimulation or to an internalized extension cable and subsequently to the implantable pulse generator (IPG).

IPGs are telemetrically programmable and are, in general, placed subcutaneously on the pectoralis muscle below the clavicle. In very thin individuals, implantation in the abdominal wall is an alternative. IPGs can either serve one electrode (Solettra(r), Itriel(r) II or Itriel(r) III, Medtronic, MA, USA), or two electrodes at the same time (Kinetra(r), Medtronic, MA, USA). Depending on the configuration of the required electrical field, stimulation in a monopolar mode (at least one contact is programmed as cathode against the neurostimulator case) or bipolar mode (two contacts are programmed as cathode and anode) is possible. Monopolar stimulation creates a radial current diffusion, covering an approximately spherical space around the stimulating electrode, bipolar stimulation provides a more focused current field with a maximal effect near the cathode¹¹¹. Even though bipolar stimulation may be helpful to minimize side effects, it is recommended to try monopolar stimulation first, because in most cases it requires lower energy to achieve the same clinical benefit as compared with bipolar programming. An excellent introduction into DBS programming has recently been published by Volkmann and co-authors¹⁴⁴.

Models of the Basal Ganglia

The most widely accepted model of basal ganglia function bases upon primate experiments¹⁴¹. It is a helpful construct to understand both pathophysiology of movement disorders and therapeutic relevance of commonly used stereotactic targets.

The basal ganglia are classically viewed as a family of functionally segregated circuits, that arise from the cortex; pass through striatum, pallidum, and the thalamus; and project back to the frontal cortex⁴. Of these circuits, the “motor” circuit is considered most important in the development of movement disorders such as dystonia, hemiballism, Parkinson’s disease, and tremor⁴¹. Because of its complex composition, the following will only highlight the most basic aspects of basal ganglia anatomy (Fig. 1). For further information, the author recommends recently published comprehensive descriptions of the cellular organization and anatomical connectivity of the basal ganglia^{29,52,105}.

The striatum serves as the recipient of efferents from most cortical areas, and projects by means of intrinsic pathways to both basal ganglia output nuclei, the GPi and to the substantia nigra-pars reticulata (SNr). Neurons from GPi and SNr project to the ventral motor nuclei of the thalamus that, in turn, project back to the frontal cortex. Dopamine, released from endings of neurons located in the substantia nigra-pars compacta (SNc), modulates the activity of striatal cells and, therefore, of the whole circuit. A major assumption of the model is that different dopamine receptors (D1 or D2) are localized on the different striatal neuronal populations that give rise to direct (to GPi) and indirect (to GPe = external segment of globus pallidus) pathways⁵². Under normal condition (Fig. 1A), striatal neurons projecting directly to GPi appear to be facilitated by dopamine actions on D1 receptors, whereas neurons projecting to GPe are inhibited by dopamine actions on D2 receptors.

Dopamine depletion in the striatum, as it is the case in Parkinson’s disease (Fig. 1B), gives rise for both a reduction of activity of the direct inhibitory pathways, and an increase of the activity in the indirect excitatory pathway, synergistically leading to an increased GPi activity. Because the GPi-thalamic projection is inhibitory, increased GPi discharge leads to inhibition of thalamocortical neurons. The resulting reduction of cortical activation would then account for the hypokinetic signs of PD. Another anatomical structure, which might be involved is the pedunculopontine nucleus (PPN), representing the principal site of the loosely defined mesencephalic locomotor region (MLR). Because upper brainstem centers receive dense inhibitory inputs from GPi and SNr, it seems possible that akinesia in PD may be due to GPi and SNr inhibition of these structures¹³. From that point of view, lesions or stimulation within GPi or STN will reduce the increased activity, therefore improving hypokinetic symptoms of PD.

Also the hypothesis that specific oscillating properties of thalamic cells might provide the basic mechanism of central

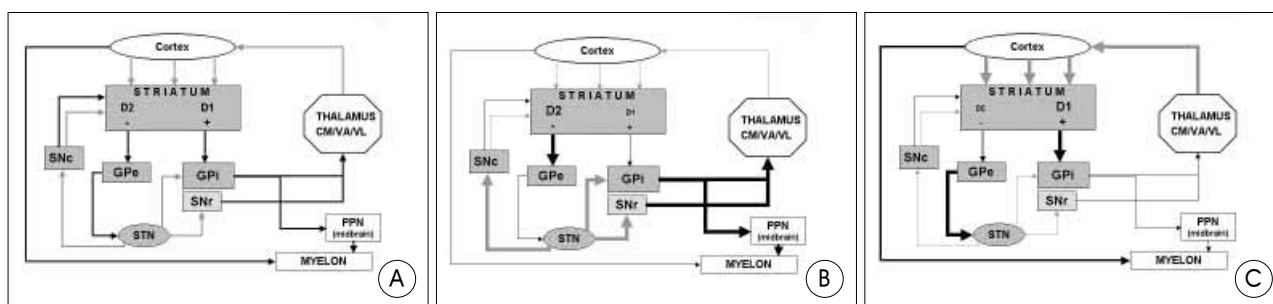


Fig. 1. Scheme of basal ganglia circuitry adopted from references^{1,4,41}. A : normal ; B : Parkinson's disease; and C : dystonia as an example for hyperkinetic movement disorders. Grey lines represent stimulating pathways, whereas black lines stand for inhibitory ones. Thicker lines indicate increased neuronal activity and thinner lines decreased neuronal activity. Abbreviations: D1, D2: dopamine receptor subtypes one and two; GPe: globus pallidus externus; GPi: globus pallidus internus; PPN: pedunculo-pontine nuclei; SNc: substantia nigra pars compacta; SNr: substantia nigra pars reticulata; STN: subthalamic nucleus.

tremor⁸⁹) fits loosely into this model. Given that the oscillatory mode of thalamic cells is driven by hyperpolarization of thalamic cells, as GPi and SNr are overactive in PD, the inhibitory input to the thalamus might hyperpolarize the thalamic cells, thereby causing this mechanism to be activated³⁴). Beside the thalamus, in patients as well as in animals tremor cells were found inside STN and GPi. They could either be the generators by themselves or they may be an integral part of an unstable oscillating network. In this case, not a single nucleus by itself is responsible for tremor generation, but synchronized action of cells regulating one functional region or even from different regions. In contrast to normal conditions where the dopaminergic input is believed to keep cells separated they get synchronized in PD¹¹²). Significant alleviation of tremor following lesioning or stimulation inside GPi or STN might be due to a desynchronization of the rhythmic activity within the oscillating loops.

Based on the phenotype of dystonia i.e. the presence of excessive involuntary movements this disease has in contrast to the hypokinetic PD commonly been considered as a hyperkinetic movement disorder. To explain both conditions, the Alexander/DeLong-mode¹⁴), which is also called the “rate model”, uses the level of the mean discharge rates inside GPi. These rates are increased in the hypokinetic disorder PD, consequently the opposite has been assumed for hyperkinetic disorders. In contrast to PD, the motor thalamus is released from pallidal inhibitory influx, facilitating the initiation of complex cortical motor programs without substantial control, which in consequence induce involuntary movements (Fig. 1C). The rate model, however, does not explain why ablative surgery or DBS interruption in an already suppressed part of the basal ganglia reduces hyperkinetic activities.

Vitek recently proposed a modification of the rate model taking into account physiological data¹³⁹) and hypothesized

that three main processes are involved in the induction of hyperkinetic movements:

- (i) Changes in temporal coding: Temporal coding provides a more precise representation of information transmission in neural systems and sets the appropriate conditions for the firing of those neurons, whose discharge may critically influence the discharge properties of neurons to which they project⁴⁷). Thus changes in neuronal activity that begin in the basal ganglia are likely to disrupt the spatio-temporal pattern of synaptic afferent activity at the level of the cortex, alter the level of excitability of cortical neurons changing their response to afferent input, leading to errors in cortical output and resulting in disordered motor control. Abnormalities in the functional organization of the motor cortex have been documented in dystonic conditions using transcranial magnetic stimulation^{8,36,49,66,114}).
- (ii) Changes in defocusing of sensory input: Dystonic patients are obviously unable to selectively activate specific muscle groups by defocusing sensory input from the periphery to the sensorimotor cortex. This hypothesis is in line with the registration of widened receptive fields in the pallidum and thalamus in these patients^{41,84,92,138}).
- (iii) Uncontrolled increases in synchronization: Increases in synchronization of neuronal activity may up to a certain level occur under normal conditions¹¹⁵). Uncontrolled increase, however, involving a critical population of neurons in GPi may provoke similar synchronous activities throughout the pallido-thalamo-cortical circuit, resulting in the well known involuntary movements¹³⁸).

A modified version of the rate model should also consider reports about loss of inhibition of various spinal and

brainstem reflexes in patients with dystonia⁵⁹⁾, which likely reflects alterations in descending projections to inhibitory neurons, that are indirectly modulated by activity in the pallido-thalamo-cortical motor circuit.

Mechanisms of Deep Brain Stimulation

Even though DBS has become an established therapeutic alternative to ablative surgery there is still an ongoing debate about the mechanisms underlying the effect of high frequency electrical stimulation. The immediate cessation of tremor caused by DBS and the delayed response of dystonic symptoms might be indicative of the notion that different mechanisms may be involved. Main questions are addressed to the structures which are most likely affected by the current - axons or neurons - and if DBS is excitatory or inhibitory.

In general, electrode polarity, pulse width, and current amplitude are stimulation parameters determining which neural elements in the surrounding of a stimulating electrode are being recruited¹⁴⁹⁾. From the studies performed by Ranck it is well known, that electrical stimulation is more likely to activate large myelinated fibers before small axons or cell bodies, axons near the cathode before those near the anode, and axons oriented parallel to the electrode before axons oriented transversely¹¹¹⁾. Clinical studies that determined the chronaxie of DBS-induced effects support the concept that the predominant effect of stimulating in the motor thalamus, GPi or STN is probably due to activation of large axons^{12,63, 147)}. In anatomical localization studies performed after implantation of electrodes into the STN of patients, even though the tip of the quadripolar electrode was precisely placed inside the target in most cases, the electrode contact, which induced the best clinical effect was selected proximally to the tip projecting onto the dorsolateral nucleus-fiber interface or even inside white matter surrounding the STN^{118, 141)}. These findings indicate a high probability for activation of axons of the projection neurons and/or the axons of the afferent inputs into a given nucleus (as well as fibers of passage in or near the nucleus), which in turn could modulate both neurons in the nucleus or those in other regions or could lead to the release of neurotransmitters from axon collaterals in other nuclei.

Studies performed in the normal brain of rats to investigate the effects of STN stimulation gave some evidence for both inhibition of STN neurons^{24,25,32)} and increased firing of STN neurons¹⁴⁶⁾. These findings are not contradictory, if one considers that a complex pattern of inhibition and activation of neurons may result from different distances from the

stimulated site as it has been demonstrated during thalamic stimulation¹²¹⁾ and that axons may fire independently of the soma during extracellular stimulation⁵⁵⁾.

Treatment Planning

In contrast to tumor treatment, functional stereotactic operations are highly elective procedures. This point, the small size of the targeted areas and their anatomic location within eloquent parts of the brain necessitate extreme accuracy of both treatment planning and surgical devices. Only the combination of optimum imaging together with rigid fixation of the patient's head in a stereotactic frame meets these requirements.

Target coordinates are historically taken from a stereotactic brain atlas, in whom the position of anatomical structures is defined in relation to a line connecting anterior commissure (AC) and posterior commissure (PC) (AC-PC line) and in relation to the wall of the third ventricle. This information is then transferred into ventriculography, stereotactic CT and/or MRI. Transfer from atlas data into a particular patient requires mathematical correction of differences between model and individual brain related to the length of AC-PC line, thalamus height and width of the hemisphere.

The exclusive use of the two-dimensional ventriculography is obsolete because it does not adequately allow to control trajectories in relation to anatomy. Given that MR-imaging guarantees precise definition of the AC-PC line, ventriculography is no more a prerequisite for targeting. Because of its limited image resolution with respect to both definition of the AC-PC line and control of trajectories, the exclusive use of CT-based stereotaxy can not be recommended. At the moment, stereotactic MRI provides maximum anatomic resolution, the option to precisely define the AC-PC line, to directly delineate the boundaries of the STN, and to a certain degree define boundaries and subunits of the pallidum. Depending on the sequence selected for data acquisition, different anatomical structures of interest can be contrasted. An ideal setting is threefold, with two standard sequences for the control of trajectories (ideally T1- and T2-weighted images) and a third sequence, which contrasts the target and adjacent structures.

The major limitation of MRI is distortion. Although in the meantime most of scanner generated inhomogeneities can be eliminated by adequate data acquisition and phantom measurements, there remain susceptibility artifacts i.e. inhomogeneities caused by the scanned object itself^{14, 94, 129)}, which are difficult to correct¹²⁹⁾. A simple solution for this problem is image fusion of preoperative non-stereotactic MRI with intrao-

perative stereotactic CT⁴⁵⁾ creating stereotactic MR-images with automatic correction of almost all susceptibility artifacts. High resolution imaging should be combined with a software enabling the surgeon to calculate the target and control the trajectory three-dimensionally and in a multiplanar mode. X-ray tubes installed in the operating room (telerradiography) enable the surgeon to precisely control and document the position of e.g. stimulation electrodes.

Targets

At the moment, three targets are used for DBS of movement disorders: (i) the ventral motor area of the thalamus (ventrointermedius nucleus (Vim) or ventrooralis posterior nucleus (Vop), according to Hassler's nomenclature⁶¹⁾, which corresponds to the posterior part of ventral lateral (VL) nucleus in the outlines of thalamic subdivisions, given by Jones⁷⁰⁾, together with the subthalamic region (cerebello-thalamic and pallidothalamic connections, and zona incerta (ZI)), (ii) the ventro-postero-lateral (VPL) part of the internal globus pallidus (GPi), and (iii) the subthalamic nucleus (STN).

Motor thalamus

This term when used in a restricted sense is reserved for the ventral thalamic region with cerebellar and basal ganglia (pallidal and nigral) afferent territories⁶⁷⁾. Functionally, the thalamus is involved in the tremorgenesis of the various types of tremor. It functions as a relay nucleus in (i) the corticobasal ganglia-thalamocortical loop in parkinsonian tremor, (ii) the premotor cortex and cerebellar-thalamic connections in cerebellar types of tremor, and (iii) the premotor cortex and connections of the triangle of Mollaret⁵⁷⁾ in essential tremor and brainstem tremor, or Holmes tremor⁴⁴⁾.

Basing upon theoretical considerations, Hassler inaugurated the oral thalamic nuclei for PD surgery⁶⁰⁾. As a consequence, most neurosurgeons targeted the Vop and Vim and particularly the ventral entry zone of the dentate-thalamic fibers. Others like Mundinger preferred the subthalamic area aiming directly at cerebellothalamic or pallidothalamic fibers⁹⁸⁾. In light of targets, in whom DBS improves almost all symptoms associated with PD (GPi, STN), thalamic stimulation is exclusively reserved for tremor therapy.

Thalamic targets are not directly visible on MR images but can be defined using atlas coordinates and ventricular landmarks (AC-PC line, wall of third ventricle). For calculation of the laterality a width of the third ventricle in the order of 6-10 mm is supposed. Larger third ventricles may give rise for inaccuracies due to lateralization of thalamic nuclei. Electrop-

physiological exploration of the motor thalamus during surgery (lesioning or electrode implantation for DBS) revealed that what is called "Vim-surgery" corresponds to the anterior border of the Vim and the posterior border of Vop. Related to the cranio-caudal extension it is the lower part of Hassler's Vim and Vop^{23,131)}. According to the stereotactic atlas of Schaltenbrand¹²⁰⁾ the base of Vim is located on the AC-PC line, 7.5 mm anterior to PC and 14.5 mm lateral to ACPC-line if the width of third ventricle is 6 mm. The area below the thalamus (= subthalamic region) is reached when the same trajectory is lengthened for 2-3 mm. For two anatomical reasons, one or two contacts of the quadrupolar electrode (model 3387) should be placed in this subthalamic area: (i) Subcortical afferents particularly connections between dentate nucleus and motor thalamus (dentato-thalamic fibers) are bundled at the ventral border of Vim⁶¹⁾. (ii) The ZI is reciprocally connected with several cortical areas, the upper brainstem, cerebellum, and thalamus^{101,110)}. Own clinical observations and single reports from the literature confirmed these theoretical considerations indicating that substantial tremor improvement particularly in PD, ET, and proximal tremor associated with posttraumatic tremor or multiple sclerosis is achieved with electrode contacts below the ventral base of the motor thalamus^{7,71)}.

Globus pallidus internus

According to the stereotactic brain atlas from Schaltenbrand and Wahren stereotactic coordinates used in general, are given with: 2-3 mm in front of the midcommissural point (MCP: the midpoint of the AC-PC line), 20-22 mm lateral from the midline of the 3rd ventricle, and 3-6 mm ventral to the AC-PC line. Visualization of anatomical landmarks like optic tract, medial border of the putamen, and the internal capsule together with details of subdivisions of the pallidum including GPi, lamina medullaris interna, GPe, and lamina medullaris externa, which in addition to atlas coordinates should be used for final adjustment of the targeted area can be achieved by the acquisition of either Turbo spin-echo proton density sequences or Turbo true-inversion-recovery sequences.

Using microelectrode recording in patients, somatotopy of kinesthetic representation inside GPi has been documented with the majority of cells located posterolaterally in the nucleus. Within this region the leg was represented more dorsally than the arm, and the face (jaw) mainly ventrally⁵⁸⁾. Following DBS in PD, two study groups observed different clinical effects for the dorsal and ventral GPi stimulation^{18, 73)}. Dorsal stimulation had a marked anti-Parkinsonian effect,

which may induce rather than suppress dyskinesia, and was attributed to additional stimulation of the GPe¹⁴⁸). Ventral stimulation of GPi worsened akinesia and blocked the beneficial effects of levodopa on bradykinesia and gait, while improving rigidity and markedly suppressing dyskinesia. Regarding a segmentation of the GPi into an inner and outer segment and the large fiber bundles which correspond to these subunits (ansa lenticularis: fibers arising from the outer portion of GPi and running at the ventral border of the pallidum; lenticular fasciculus: arising from the inner portion of GPi and running at the dorsomedial margin of the pallidum), Krack et al. hypothesized that the inner portion of the GPi might be involved in the pathophysiology of akinesia and the outer portion in that of rigidity⁷³). Furthermore these authors defined the central portion of GPi as the probably optimal site for DBS in PD.

In patients with dystonia, a specific pattern of clinical effects correlating with stimulation in different parts of the GPi has not yet been described. However, taking into account the direct effect of pallidal DBS on levodopa induced dyskinesia in PD, it makes particularly in dystonic patients sense to have one of the four electrode contacts just above the optic tract in the ventral part of GPi.

Subthalamic nucleus (STN)

According to the stereotactic Schaltenbrand atlas this target has the following coordinates 2-3 mm behind MCP, 3.7 mm below this point rectangular to AC-PC line, and 12 mm lateral of the midline of the 3rd ventricle. The STN is also directly visible in strong T2-weighted sequences, on axial sections as well as on coronal sections. It appears as a hyperintense signal lying above the SNr, anterior and lateral to the red nucleus and medial to the pyramidal track.

In comparison to Vim or GPi, localization of the STN is more complex because of its lens shape, its small dimension (approximately 10 mm rostrocaudal, 10.5 mm mediolateral, and 7 mm dorsoventral), and its oblique orientation with respect to the three anatomical axes. Also the functional organization inside the STN is very complex. Beside inhibitory pallidal affents, this nucleus receives also excitatory input from the cerebral cortex, the PPN, and the parafascicular nucleus, which is part of the intralaminar thalamic structure. Functional-anatomically, the ventro-medial STN contains the associative and/or limbic connections and the dorso-lateral part the somatosensory/somatomotor connections⁴⁶). Taking into consideration the division of the nucleus into motor and limbic areas as well as the results of postoperative localization studies^{118, 141}), it is recommended to place the tip of the

stimulation electrode more dorsally and laterally inside the STN.

Electrophysiology

Together with their first stereotactic operation in a human being, Spiegel and Wycis introduced the electrophysiological exploration of the radiologically defined anatomic target, which constituted in these days perhaps the most important step to avoid neurological complications in functional stereotaxy¹²⁸). Despite the enormous advances in brain imaging since then, there is still need for intraoperative electrophysiology. However, regardless of the technique applied (e.g. macrostimulation, microelectrode recording, microstimulation), the physiological exploration should not be conducted in absurdum. In other words, the best electrode placement is of no value if at the end the patient is hemiplegic or even dies. In the following the main procedures and their relevance for functional stereotaxy will be briefly commented.

- (a) Macrostimulation: The test electrode is primarily introduced on the same trajectory as planned for the definitive stimulation electrode. Currents at different frequencies and duration (ranging from 0.1 - 0.5 msec) with an electrical intensity ranging from 1-5 mA are applied. A routine schedule should contain very low frequencies (≤ 10 Hz), which interfere with and may worsen symptoms (e.g. tremor) or may provoke side effects from structures adjacent to the target (e.g. response from internal capsule or ruber nucleus) and high frequencies (100-200 Hz), which due to their suppressing character may improve disease associated symptoms.
- (b) Microelectrode Recording (MER): Modern equipment allows the introduction of multiple, parallel arranged electrodes and thus mapping of a particular area. Arguments for the procedure are the fine degree of localization provided by MER and research insight into the individual properties and population characteristics of neurons, which in turn provide important insight into the pathophysiology of a particular disease. These advantages have to be balanced against the potentially increased risk associated with MER. Recent reports^{83,88, 102,119,124}) gave surprising high rates of severe complications, mainly hemorrhage with an associated morbidity ranging from 3.8-11.5%^{102,119,124}) and a mortality ranging from 3.8%-7.5%^{119,124}). An additional risk of MER is undoubtedly a prolongation of the operation

time if compared to macrostimulation which may subsequently increase the risk for infections and substantial brain shift.

If microrecording in combination with microstimulation is required, is still a matter of debate. Most systems which are commercially available allow with the same electrode microrecording and microstimulation.

Several studies addressed the effect on MER on the accuracy of target localization. As a consequence of MER guidance, Alterman and coworkers using an MR-based planning system for performing pallidotomies in advanced PD changed in 98% of their cases the final position of the lesioning probe. In 12% of the patients, the distance moved was greater than the diameter of the lesion made (i. e. 4 mm)⁶. For STN-DBS, Zonenshayn et al. reported that direct MRI targeting was the least accurate method and that MER together with all methods additionally integrated in their setting (e.g. digital atlas) had a significant impact on the accuracy of the final electrode position¹⁵⁰. In contrast, from 1996 through 2000 our group preformed stereotactic placement of stimulation electrodes exclusively with CT/MR-fusion and macrostimulation (one trajectory). The clinical outcome of our patients presenting with PD was in the same order (STN DBS) or even better (GPi DBS)^{142,143} if compared to those groups which implanted electrodes for DBS using MER guidance.

Clinical Data

DBS of Ventrolateral Thalamus (Vim/Vop) for the Treatment of Tremor

(a) Parkinson's disease and Essential Tremor (ET)

Reviewing the literature, chronic stimulation gained excellent and stable tremor suppression in 80-100% of the patients with PD (Table 1). Parkinsonian motor symptoms others than tremor were only inconstantly influenced. Limousin et al. described significant reduction of both rigidity and akinesia contralateral to the implantation side. Rehnrona et al. found an improvement of akinesia, Tasker et al. some reduction of rigidity. Others reported no effects on rigidity and akinesia^{2,23}. There are also single observations about improvement of Levodopa induced dyskinesia^{35,132}. However, these general effects of thalamic DBS are not comparable to those gained with GPi- or STN-DBS.

Also patients with ET presented with a favorably good

outcome (Table 1). Only two investigators observed comparably lower response rates with 61% tremor suppression at 6 months²³ and 71% at 6-7 years postoperatively¹¹³. Moderate head tremor associated with ET was significantly improved at the earliest 3 months after surgery and was through bilateral DBS more affected if compared to unilateral procedures⁸⁷. In the experience of Taha and coworkers, thalamic DBS was able to suppress head tremor completely or almost completely in 9/10 cases. Additionally, 6 of 7 patients experienced improvement of their voice tremor¹³⁰. A general feature of tremor therapy with thalamic DBS was a severe tremor of higher frequency which occurred when the stimulator was switched off^{23,35,87,113}. This "rebound phenomenon" was more frequently observed in PD (40-42%) than in ET (about 20%)^{23,87}.

Stimulation parameters did not substantially differ between patients with PD or ET. For mean values the following ranges are taken from the literature: amplitude. 2.2-3.6V, stimulation frequency: 130 - 181Hz, and pulse width; 60-256 μ sec. Because of a microthalamotomy effect and/or localised edema around the electrode tip, stimulation parameters have to be adjusted during the first weeks following surgery^{23,103,132}. There are single reports of cases with a microthalamotomy effect lasting for up to months or even years^{113,132}. Related to longer follow-up times, Alesch et al. observed no tolerance development. Others documented a significant increase of the amplitude within the first year^{72,86}. Rehnrona et al. reported significant increment of stimulation frequency only for patients with ET¹¹³. In the prospective comparative study of Schuurman et al. 68 patients (45: PD, 13 ET, 10: MS) were selected and randomized either for thalamotomy or thalamic DBS¹²³. Pre- and postoperative tests included quantification of tremor severity, stage of disease, and patient's functional status. Briefly, this study demonstrated that both modalities effectively suppressed tremor. However, in comparison to thalamotomy DBS resulted in a greater improvement of function and was associated with a lower rate of adverse events. After retrospective comparative analysis of their patients Tasker et al. basically confirmed this estimation¹³².

(b) Multiple sclerosis (MS)

Considering only those articles dealing with a minimum number of five patients, six study groups addressed the treatment of action and postural tremor of MS with DBS

Deep Brain Stimulation

Table 1. Effects in clinical studies treating tremor with Vim DBS

Author/year	Improved pts.* /total no. pts.	FU	Study design	Treated tremor forms
Benabid/1991	38/43 (88% of thalami implanted)	mean: 13 m	retrospective	PD, ET
Blond & Siegfried/ 1991	19/19 PD 2/2 ET	not reported	retrospective	PD, ET, dyskinetic T
Caparros-Lefebvre/ 1993	8/10 (80%)	22–34 m	NG	PD
Alesch/1995	31/33 (94% of thalami implanted)	3–48 m	retrospective	PD, ET
Benabid/1996	88% [104/118] PD 61% [18/30] ET thalami at 6 mth	0.5 – 8 yr	prospective	PD, ET, cereb. T
Geny/1996	9/13 (69%)	8–26 m	retrospective	cereb. T (MS)
Koller/1997	71% [17/24] PD 90% [26/29] ET	3 m 1yr	multicenter, blinded eval.	PD, ET
Ondo/1998	19/19 PD 14/14 ET	3 m	prospective, blinded motor evaluation	PD, ET
Whittle/1998	5/8	N.G.	prospective	cereb. T (MS)
Limousin/1999	63/74 (85%) PD 33/37 (89%) ET	12m	prospective	PD, ET
Montgomery/1999	14/15	< 3 – > 12 m	prospective	cereb. T (MS)
Shulder/1999	3/6	> 6 m	retrospective	cereb. T (MS)
Taha/1999	22/23	10 m	retrospective	PD, ET, cereb.T
Hooper/2002	10/10	12 m	prospective	cereb. T (MS)
Berk/2002	60% at 12 mth (total no pts: 12)	12 m	prospective	cereb. T (MS)
Rehncrona/2003	12/12 PD 10/13 ET (77%)	6–7yr	retrospective blinded re- evaluation	PD, ET
Comparative Studies : Tremor Therapy with Thalamotomy (TT) or Thalamic–DBS (T–DBS)				
Tasker/1997	77% (17/22 TT) 94% (15/16 , T–DBS)	3 m – > 5yr	retrospective	PD, ET, cereb.T
Schuurman/2000	97% (33/34 TT) 94.% (32/34 T–DBS)	6 m	prospective, randomized	PD, ET, cereb.T

* Improvement summarizes complete and partial response. Abbreviations: ET: Essential Tremor; FU: follow-up; PD: MS: Multiple Sclerosis; m: month(s); N.G.: not given; Parkinson's disease; pts: patients; T: tremor; yr: year(s)

(Zitate). In three retrospective studies a total of 33 patients were evaluated. At 3-12 months postoperatively both tremor and simple functional manoeuvres of the contralateral upper limb were improved^{51,96,125}. Geny et al. concluded that the final result depends mainly on the individual preoperative status⁵¹. Three prospective protocols selected a total of 27 patients for thalamic DBS. Even though at 12 months postoperatively tremor suppression was still significant^{27,123}, effects on the functionality of the upper limbs were only inconstantly observed. Whilst in one study 6/9 cases presented with

still ongoing improvement⁶⁴, two investigators documented no functional improvement at his time^{27,123}. Main reasons which may be responsible for the worse results in MS if compared to other tremor forms may be the following: (i) DBS improves only tremor and not the ataxic components. In other words, successful tremor suppression may unmask ataxia²⁷. (ii) The course of the underlying disease is rapidly progressive, consecutively balancing any initial good response within a short time period. This estimation is supported by a frequently observed development of “tolerance” within the first

postoperative year⁹⁶. (iii) The pathophysiology of tremor in multiple sclerosis is not yet precisely defined.

According to the literature¹²³ and our own experiences, MS patients who might be candidates for DBS should fulfill the following criteria: (i) Immediately before surgery, the disease should have been stable over a minimum time of 6 months. (ii) The tremor should not have any significant ataxic component. (iii) The patients should not have additional neurologic deficits like arm paresis, nystagmus, and/or severe head tremor which even if the tremor is completely suppressed may hinder functional improvement.

The most frequently observed side effects of thalamic DBS were paresthesia, when the stimulator was switched on (4-100%), dysequilibrium (3-13%), foot or hand dystonia (1-10.5%), and dysarthria (3-23%) (Table 2). Most complications were either transient or disappeared when stimulation parameters were readjusted.

DBS of Globus pallidus internus (GPi) or Subthalamic nucleus (STN) for the treatment of Parkinson's disease

To select patients for either GPi or STN DBS, a modification of the CAPIT (Core Assessment Program for Intracerebral Transplantation) protocol is frequently applied⁸². In our own clinical protocol¹⁴² the following inclusion criteria have been defined (i) L-DOPA responsive PD, (ii) complications of long-term L-DOPA treatment (dyskinesia, ON-OFF fluctuations), and/or (iii) symptoms resistant to optimized medical therapy (= L-DOPA, plus dopaminergic agonists plus COMT-blocker). Exclusion criteria have been: (i) previous brain surgery, (ii) other uncontrolled medical conditions, (iii) abnormal brain scans (except mild to moderate atrophy), (iv) active psychosis, and/or (v) clinical diagnosis of dementia.

Both STN and GPi DBS are effective in improving the cardinal motor symptoms of PD (bradykinesia, rigidity and tremor), both improve midline symptoms (gait, balance and "off" freezing), increase the percent of "on" time and decrease the amount and severity of drug-induced dyskinesia. The effect of stimulation on motor symptoms quantified with the Unified Parkinson's Disease Rating Scale (UPDRS) motor subscore (part III) ranged in the literature from 6% worsening to 67% improvement for GPi and from 22% - 71% improvement for STN (Table 3). Even though the mean improvement was lower in the GPi group (37%) compared to

the mean value of published STN data (52%) the maximum benefit reported for each was not significantly different. The greatest reduction of the UPDRS III motor scores gained with GPi DBS was 67%¹⁴², while the greatest reduction following STN DBS was given by Krack et al. with 71%⁷⁴. GPi DBS acts directly on L-DOPA induced dyskinesia and is therefore independent from reduction of medication whilst in the case of STN-stimulation medication has to be reduced for the relief of dyskinesia.

In most studies pallidal stimulation was able to alleviate tremor (action and rest tremor) in the order of 73-100%^{18,33,40,53,142}. Only two groups reported lower improvement (35%-40%¹³⁴). Tremor reduction during STN DBS was at least as effective as with GPi DBS ranging from 74% - 86%^{31,33,40,48,79,95,116,127,134}. Side effects caused by stimulation (paresthesia, balance impairment, dysarthria, dysphagia, dyskinesia (mainly STN), visual sensations (only GPi)) were transient and disappeared after adjustment of the stimulation parameters. The 2001 report from the DBS study group gave the following frequencies for permanent adverse symptoms due to stimulation: (i) dyskinesia (STN:2/98; GPi:3/38), (ii) diplopia (STN:2/98), (iii) dystonia (2/38), (iv) dysarthria (STN 1/98), and (v) paresthesia (STN: 1/98) (DBS for PD study group 2001). Permanent worsening of dysarthria and/or hypophonia were also documented by others following STN stimulation (frequency range: 5-56%^{86,95,116,143}). Eyelid apraxia seemed to be another characteristic side effect of STN-stimulation occurring in 25%⁸⁶ or 13%¹⁴³ of the patients.

Change of body weight after GPi DBS was addressed in one publication¹⁴², in whom 6 of 9 cases gained their weight in the order of 2-8 kg. Following STN DBS, body weight increased in 72-100% of the patients^{48,86,91,97,116,143}. The range of mean values was 4.2-8 kg^{48,86,97,116}. Severe (> 10 kg) and still ongoing weight gain was documented for 6/16 evaluated cases by Volkmann and coworkers¹⁴³. Others estimated this side effect as being "troublesome" in 4 of 7 patients⁹⁷. Increased weight might be an indirect effect of decreased hypermotility or directly caused by stimulation itself. Modulations of mood were more frequently reported for STN DBS than for GPi DBS. Apathy and abulia following GPi DBS was observed in one case⁴². Tronnier and coworkers documented severe depression in one patient which gave rise for a complete stop of DBS and a strong increase of libido in another case¹³⁵. Reactions frequently seen after STN DBS were depression^{19,43,81,143}, apathy^{43,117,143}, or abulia^{86,95,143}. Some patients presented with anhedonia¹⁴³, hypersexuality^{116,135} or manic psychosis^{81,116}. These psychiatric problems were mostly transient in the immediate postoperative course lasting

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Table 2. Complications / Adverse effects in clinical studies treating tremor with Vim DBS

Author/year	Complications related to surgery	Hardware	DBS
Benabid/1991	not observed	not observed	paresth./limb dystonia: 27% dysequil./dysarthria: 14%
Blond/1992	NE	NE	dystonia foot: 10.5% dysequilibrium: 5%
Caparros-Lefebvre/1993	NE	NE	dystonia hand 2/10 (20%)
Alesch/1995	hemorrhage: 3.7% infarction: 3.7%	not observed	paresthesia: 7.5% dysequilibrium: 3.7% dysarthria: 22%
Benabid/1996	hemorrhage: 0.9% infection: 2.6%	seroma: 1.8%	paresthesia: 9% dystonia foot: 9% dysarthria: 19.6%
Geny/1996	asthenia: transient paresis:	not observed	paresthesia: all
Koller/1997	hemiparesis: 3.8%. lead dislodge. 1.9% seizure: 1.9% infection: 1.9%	IPG malfunction: 1.9% skin erosion: 1.9%	trans. paresthesia: almost all dysequilibrium: 3.8%
Tasker/1997	edema/HP: 5% ipsilateral TIA: 5%	extrusion % lead dislodge 5%	paresthesia: 5%
Ondo/1998	no significant complications	lead fract: 6%	all transient: dysequilibrium: 9% dysarthria: 3% paresthesia: 9% headache, nausea, diplopia, altered mental status (frequency of each item 3%)
Whittle/1998	NE	NE	NE
Limousin/1999	hemorrhage: 3% infection: 2%	seroma: 2%	dysequilibrium: 3% dysarthria 6% dystonia 1% (all transient)
Montgomery/1999	hemorrhage: 6.7%	not observed	not observed
Shulder/1999	no side effects	not observed	not observed
Taha/1999	not observed	not observed	dysequilibrium: 13% dysarthria: 8.7%
Schuurman/2000	mortality: 2.9%	not observed	dysarthria: 7/34 (22%) dysequilibrium: 5/34 (14.7%) dystonia: 2/34 (5.9%) arm ataxia: 3/34 (8.8%)
Hooper/2002*	hemorrhage: 13.3% (CT-findings) seizure: 13.3% infection 6.7%	not observed	paresthesia: "some" pts.
Berk/2002	transient paresis 24% infection: 24%	not observed	paresthesia: all
Rehncrona/2003	not observed	lead fracture: 4%	paresthesia: 4%

*37 pts. referred and assessed for DBS, but only 15 underwent surgery. In 10/15 implantation of the total system completed (in 3/15 cases no target detectable intraoperatively) Abbreviations: DBS: deep brain stimulation; NE: not evaluated; TIA: transitory ischemic attack;

for a few weeks and might be related to acute withdrawal of dopaminergic medication. With longer follow-up STN stimulation seems to have rather an antidepressive effect^{122,143}. This estimation is in line with improvements of the Beck Depression Inventory^{11,33,81}. Quality of life was addressed in a comprehensive analysis of the Grenoble group⁸¹ including 60 patients with bilateral STN implants. Twelve months after surgery all aspects of health related quality of life in PD, including emotional and social functioning had significantly improved. Because moderate improvement in the BDI did not correlate with the quality of life improvement, the authors concluded that in their study motor complications seemed mainly to determine quality of life.

Other effects of bilateral DBS on neuropsychological behavior were only inconstantly observed. One evaluation for GPi DBS⁶⁹ and 4 investigations attracted to STN DBS^{86,91,107,127} documented no change of specific tests. Burchiel et al. found, in general, no statistically significant difference between the groups in their randomized study (GPi vs. STN DBS), but improvement in the Cognitive Difficulties Scale. Specific tests were also not impaired in one comparative study¹⁴³. Decreased verbal fluency occurred together GPi DBS^{53,142} and STN DBS^{3,11,133}. Improvements of the Trail-Making A and/or B Test for both GPi and STN DBS^{3,11} suggests a positive effect of this therapy on dorsolateral prefrontal cortex function.

For several reasons, it became widely accepted to prefer the STN over GPi as primary target. One striking argument is the energy to gain maximum clinical improvement which is significantly lower in the STN than in the case of pallidal stimulation. Additionally there are two published cases, which give some evidence for tolerance development 27 and 39 months after initial good response of GPi stimulation. Replacement with bilateral STN stimulation was again successful⁶⁵. Own experiences in 3/11 cases (replacement of GPi stimulation by STN electrodes 3-4 years after initial surgery) confirmed this observation (unpublished data). Also the fact that STN-stimulation allows significant reduction of specific medication seems to be in the first view highly attractive but can also give rise for difficulties: (i) Adjustment of dopaminergic medication in relation to stimulation prolongs postoperative hospitalization. (ii) Besides motor symptoms a subgroup of patients is at the same degree disabled by non-motor disturbances (e.g. hypersalivation, vegetative instability). Because STN stimulation requires reduction of medication which in consequence might narrow the therapeutic window for dopaminergic therapy, parkinsonian symptoms, which are alleviated less by stimulation

than drug therapy, may be unmasked. As a result, in many STN-stimulated patients, therefore, remain mild hypophonia or hypersalivation^{95,116,143}. Theoretically, a narrow window for specific drug therapy, could also become problematic with further progression of disease.

Globus pallidus internus (GPi) stimulation for the treatment of dystonia

Already in 1977, Mundinger described significant alleviation of cervical dystonia after thalamic stimulation⁹⁹. Unfortunately, this study was never published in English and the promising results gained with this technique were not recognized. In 1999 when pallidotomy had been shown to positively influence dystonia, DBS has been introduced for the treatment of this disease^{38,75,80}. Since that time a low but steadily increasing number of publications were presented. Because all reports base upon a comparably low numbers of patients they should be interpreted cautiously.

Similar to pallidotomy⁵, the response after GPi DBS seems to depend on etiology. Improvement in primary generalized dystonia was superior to secondary generalized dystonia. Regarding the first group it is generally agreed that DYT-1 positive cases can expect a higher benefit (particularly children) with improvements of up to 90% on the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS)^{26,39,135,136}.

All components of cervical dystonia (pain, dystonia, and function) were improved in three patients who were unresponsive for botulinum injections⁷⁵. These results have been reproduced by others^{9,68,106} and again by Krauss et al. in 2002 for a slightly expanded series of patients (five individuals⁷⁶). In contrast, Kulisevsky et al. observed a dissociated response with pain reduction but no significant improvement of dystonic motor symptoms⁷⁸.

There is little experience with dystonic syndromes of rare etiologies. The improvement of choreoathetosis secondary to cerebral palsy in a severely disabled 13-years old boy was excellent¹⁰ whilst in an 11-years old boy only "hyperkinetic elements" responded substantially to pallidal DBS and improvement of dystonia was moderate⁵⁴. Krauss et al. presented a 2-year follow-up of four patients⁷⁷. The gain of functionality (23% on the BMFDRS and Unified Dystonia Rating Scale) was statistically not significant. However, these patients had an improvement in pain scores and estimated themselves as being substantially better.

In one patient with Meige syndrome, bilateral GPi DBS had a substantially greater effect than previous thalamic stimulation¹³⁶. Krauss et al. who observed an impressive improvement of blepharospasm in one case with primary generalized DYT1-

negative dystonia formulated the hope that GPI DBS might be of help for patients with isolated blepharospasm or Meige syndrome⁷⁷). The time course of response showed a great variability with immediate onset of improvement but also delayed effects. Optimal results were documented even after continued long-term DBS (up to 24 months)^{39,77,135,136}. Early relief from mobile phasic components of dystonia occurring within hours after the onset of DBS is assumed to be a good predictor for further improvement¹³⁶. In patients with primary generalized DYT1-negative dystonia one study group observed progressive improvement only during the first three months and no substantial increase of the scores at the latest follow-up (24 month). This pattern was seen contrary to experiences gained in pallidal DBS of cervical dystonia with an ongoing improvement up to 24 months.

In comparison to PD, stimulation parameters have to be more frequently readjusted during the first postoperative year. IGPs were set on a stimulation frequency which was almost the same than generally used in PD. However, some authors reported the need for substantially higher pulse width and voltage^{39,75}). Comparable to thalamic stimulation in tremor patients, the dystonic symptoms reappeared within a short time period when the stimulation had suddenly stopped.

The decision for DBS in generalized or segmental dystonia is near at hand because pharmacological treatment except for dopa-responsive dystonia is mostly unsatisfactory and the level of median improvement comparably high (up to 100%, Table 3). Weighting an average improvement of 50% against the risk of surgery in cases with cervical dystonia^{9,68,75}) DBS should be reserved for severely disabled individuals. Additionally, these patients should at first have undergone botulinum toxin injections and should be no candidates for selective peripheral denervation.

Conclusion

High-frequency deep brain stimulation is a safe and effective procedure for the treatment of movement disorders. Momentarily, three targets are considered: motor thalamus (ventrointermedius (Vim) thalamic nucleus) together with the subthalamic region (zona incerta (ZI)), globus pallidus internus (GPI), and subthalamic nucleus (STN). Vim and ZI are mainly reserved for tremor therapy. In essential or parkinsonian tremor significant and long lasting tremor suppression can be expected for 80-100% of the patients. Substantial alleviation in cerebellar tremor which

e.g. might be one complication in multiple sclerosis is not thoroughly achieved. In these cases the result and depends mainly on selection and thus on the patient's individual clinical status. Both DBS inside GPi or STN improve significantly all cardinal signs of Parkinson's disease (PD) including L-DOPA induced dyskinesias and/or severe ON-OFF fluctuations. Whilst in the case of GPi DBS the effect is directly in the case of STN DBS dopaminergic medication has to be reduced to improve dyskinesia. Reduction of medication has been one argument to prefer the STN over GPi as primary target in PD. Other striking arguments have been the energy to gain maximum clinical improvement which is significantly lower in the STN than in the case of pallidal stimulation and single observations of "tolerance" development following GPi DBS. It should, however, be mentioned that reduction of medication, which is required in STN DBS, might narrow the therapeutic window for dopaminergic therapy, which may in consequence unmask parkinsonian symptoms, which are alleviated less by stimulation than drug therapy.

Withdrawal or readjustment of medication may prolongs the postoperative hospitalization time and may be mainly responsible for the substantially higher number of patients presenting after STN DBS with transient psychiatric problems if compared to GPi DBS. Even though the conclusions base upon rather small patient series, it became evident that the GPi seems to be a target to significantly improve dystonia. Improvement in primary generalized dystonia was superior to secondary generalized dystonia. Regarding the first group it has been generally agreed that DYT-1 positive cases can expect a higher benefit (particularly children) with improvements of up to 90% on the Burke-Fahn-Marsden Dystonia Rating Scale. Side effects of DBS should be divided into surgical and stimulation associated aspects. The surgical morbidity is unequivocally lower than after ablative procedures. DBS is mainly complicated by infections, which in the worst case require removal of the system and by hardware related problems (lead fracture, lead dislocation). Most of the side effects caused by stimulation itself are either transiently or disappear after readjustment of the stimulation parameters. The main disadvantage of DBS if compared to lesioning is the high price of the stimulation devices. These costs, however, might probably be balanced by the good therapeutic effect which in consequence enables young patients to fully return to work. Studies to investigate the positive economic effects of DBS are under way.

Table 3. Clinical studies - treatment of dystonia with GPi DBS

Author/ year	No. pts./ FU	Type of dystonia	Improvement BMFDS (%) (MS/DS)	Other scores (%)	Complications/ adverse events
Krauss/1999	3pts./ 3–15m	CD	–	TWSTRS severity: 50 pain: 39 funct. disab.: 62	no
Kumar/1999	1pt/1yr	PG	65	N.E.	lead fracture, skin erosion
Coubes/2000	7pts./1yr.	PG (DYT1 +)	90,3 (60–100)	–	1/7 removal of the total system
Kulisevsky/ 2000	2pts/2yr, 17m	PC	–	VAS: 55 and 64 TS: 0 and 21	no
Lohrer/2000	1 pt./ 4yr	posttraumatic hemidystonia	improvement of: pain, phasic– dystonic movement, dystonic posture	–	no
Tronnier/2000	1pt 1pt. 1pt./ 6–12m	PD (DYT1 +) PD (DYT1 –) SD	50,5 34,5 60	– – –	dislocation of 1 electrode
Andaluz/2001	1pt./8m	PS	–	TWSTRS: 50	no
Gill/2001	1pt	ChA	postural control, disappearance of involuntary ballistic movements case reports	–	no
Parkin/2001	3pts/ 2–6m	CD	–	–	no
Vercuil/2001	1pt./1yr 1pt./ 2yr 3pts/6–12m	PG (DYT1 +) PG (DYT1 –) PG (no test)	86/86 41/43 66–70/ 50–81	– –	infection : 1/8 hemorrhage 1/16 electrodes
Voges /2001	3pts/1–3yr 1pt/3m 4pts/3–12m 2pts/3–12m	SG PG (DYT1 +) PG (DYT1 –) PS	3–72/16–60 40/15 8–25/0–40 50: 83/75: 0	– – –	no
Bereznai/2002	2pts/6m 1pt. 3pts.	SG PG (DYT1 +) PS	58: 64/42: 75 54–88 50–100	– –	transient paresis: 2/6 infection: 2/6
Krauss/2002	2pts/ 3–12m 5pts/ mean 12m	CD	–	TWSTRS: 0/92 severity: 64 pain: 50 funct. disab.: 69	no
Krauss/2003	2pts/2y 4pts/2y	PD (DYT1 –) ChA	70–78 23	UDRS: 65–70 VAS: 50 UDRS: 23	gained body weight: 2/6 lead fracture: 1/6

Abbreviations: ChA: choreoathetosis, FU: follow-up, m: months, PC: primary, cervical, PG: primary generalized, PS: primary segmental, pt(s): patient(s), SD: secondary dystonia, TS: torticollis score, TWSTRS: Toronto Western Spasmodic Torticollis Rating Scale, UDRS: Unified Dystonia Rating Scale, VAS: visual analog scale for pain, yr: years

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Table 4. Clinical studies - treatment of Parkinson's disease with either GPI or STN DBS

Author/year	Target	FU	Impl.-Mode UL/BL (no. pts.)	UPDRS III % change (OFF)	Complications/ adverse events
Siegfried 1994	GPI	6-12m	0/3	3/3 pts. improved	no
Bejjani 1997	GPI	N.E.	0/5	N.E.	N.E.
Gross 1997	GPI	1-3yr	7/0	-31	no
Pahwa 1997	GPI	minimum 3m	2/3	-21	hemorrhage 1/6 transient HP: 1/6 electrode misplacement 1/6
Tronnier 1997	GPI	2-15m	0/6	no change	no
Ghika 1998	GPI	2yr	0/6	50%	lead dislocation: 1/6 infection: 1/6
Volkman 1998	GPI	3-12mth	0/9	-66%	lead dislocation 1/9 skin erosion 2/9 infection: 1/9
Brown 1999	GPI	N.E.	0/6	-42	N.E.
	STN	N.E.	0/6	-57	
Burchiel 1999	GPI	1yr	0/4	-39	no
	STN	1yr	0/6	-44	
Ardouin 1999	GPI	3-6m	0/13	-34	N.E.
	STN	3-6m	0/49	-58	
Volkman 2001	GPI	1yr	0/9	-52	infection 8/25
	STN	1yr	0/16	-61	skin erosion 4/25 lead dislocation 4/25 lead fracture: 2/50 electr.
DBS study group 2001	GPI	6m	0/38	-33	hemorrhage: 7/143
	STN	6m	0/96	-51	infection 2/143
Kumar 1998	STN	1yr	0/7	-58	infarction: 1/7
Limousin 1998	STN	1-2yr	0/24	-60%	hemorrhage: 1/24 infection: 1/24
Moro 1999	STN	av. 16m	0/7	-36	no
Pinter 1999	STN	1yr	0/9	-47	no
Molinuevo 2000	STN	6m	0/15	-66	no
Lopiano 2000	STN	3m	0/16	-50	infection 1/16
Simuni 2002	STN	1yr	0/12	-47	hem 2/12 infection 1/12 seizure 1/12 morbidity 1/12
Figueras- Mendez 2002	STN	2yr	0/9	-49	infection 2/9
Romito	STN	1-3yr	0/22	-50	no
Lagrange 2003	STN	minimum 1yr	0/60	-55	hemorrhage 3% focal confusion 5% morbidity: 1%

Abbreviations: av: average; FU: follow-up; GPI: Globus pallidus internus; min: minimal; N.E.: not evaluated; STN: Subthalamic nucleus; m: month(s); yr: year(s); UPDRS: Unified Parkinson's Disease Rating Scale

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