ANALYSIS OF DEEP BRAIN STIMULATION AND ABLATIVE LESIONS IN SURGICAL TREATMENT OF MOVEMENT DISORDERS

WITH EMPHASIS ON SAFETY ASPECTS

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Primum est non nocere
ABSTRACT

Analysis of deep brain stimulation and ablative lesions in surgical treatment of movement disorders - With emphasis on safety aspects

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Background
The last decade has witnessed a renaissance of functional stereotactic neurosurgery in the treatment of patients with movement disorders, especially advanced Parkinson’s disease (PD), essential tremor (ET) and dystonia. Ablative lesions such as thalamotomy and pallidotomy have been gradually replaced by the technique of chronic deep brain stimulation (DBS) applied to targets in the basal ganglia and thalamus, and assumed to be more lenient to the brain than stereotactic radiofrequency lesions. Since the aim of functional neurosurgery is to alleviate symptoms of these chronic, progressive, non-fatal diseases, and to improve life quality of the patients, it is imperative that the surgical procedures remain safe and do not result in complications mitigating any anticipated positive effect of the surgery on the symptoms of the disease.

Aim
The aim of this thesis is to evaluate, compare and analyse the safety of various surgical procedures used to treat patients with movement disorders, and to document side effects and complications both peri-operatively and in a long term follow-up. Further to compare the effects of pallidotomy and pallidal DBS, and to evaluate the long-term efficacy of Vim-DBS.

Method
256 consecutive surgical procedures, 129 DBS and 127 stereotactic lesions, were reviewed with respect to complications in 197 treated patients. In a series of 119 patients operated on with DBS during a 10 year period, the occurrence of hardware related complications (infection, breakage, erosion etc) was documented and analysed. Additionally, the interference of external magnetic field with the stimulation was documented. In one patient operated on with subthalamic nucleus DBS, a highly unusual and unexpected psychiatric side effect was carefully analysed. In 5 patients operated on with both methods (lesion and DBS) on each hemisphere, respectively, the effect and side effects of each method were compared. The long term effect and side effects of thalamic DBS was analysed in a series of patients with ET followed for 7 years.

Results
There were no deaths and few severe neurological complications in this material. Unilateral ablative lesions in the pallidum were well tolerated by patients with advanced PD, while for tremor, thalamic DBS was much safer than thalamotomy, even if its effect on certain aspects of tremor could show some decrease of efficacy over time. Some of the side effects of lesioning are transient while most but not all side effects of DBS are reversible. Hardware-related complications were not uncommon especially in the early “learning curve” period, and the DBS technique, being a life-long therapy, will necessitate a life long follow up of patients. Provided safety protocols are followed and provided patient’s and carer’s education and awareness, external electromagnetic interference should not constitute a risk for patients with DBS. PD patients undergoing STN DBS should be carefully selected to avoid psychiatric or cognitive side effects, due to this brain target’s proximity to, and involvement in, non-motor associative and limbic circuitry.

Conclusions
In terms of mortality and morbidity, modern stereotactic neurosurgery for movement disorders, both ablation and DBS, is a safe procedure even in advanced stages of disease. Symptoms of PD, ET and dystonia can be alleviated mainly with DBS and even unilaterally with pallidal lesions, at the expense of, in most cases, minor side-effects.
PUBLICATIONS AND MANUSCRIPTS

This thesis is based on the following publications and manuscripts, which are referred to in the text by their Roman numerals:


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Paper IV: Acute severe depression induced by intraoperative stimulation of the Substantia Nigra. A case-report
Paper V: Pallidotomy versus pallidal stimulation
Paper VI: Thalamic deep brain stimulation for essential tremor – a long-term follow-up
ABBREVIATIONS

The following abbreviations are used in the text:

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>ADL</td>
<td>Activities of daily living</td>
</tr>
<tr>
<td>AC</td>
<td>Anterior commissure</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
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<tr>
<td>DBS</td>
<td>Deep brain stimulation</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
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<tr>
<td>ET</td>
<td>Essential tremor</td>
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<tr>
<td>ETRS</td>
<td>Essential tremor rating scale</td>
</tr>
<tr>
<td>FM</td>
<td>Foramina of Monro</td>
</tr>
<tr>
<td>Gpi</td>
<td>Globus pallidus internus</td>
</tr>
<tr>
<td>H&amp;Y</td>
<td>Hoehn and Yahr</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>ICD</td>
<td>Implantable cardiac defibrillator</td>
</tr>
<tr>
<td>IPG</td>
<td>Implantable pulse-generator</td>
</tr>
<tr>
<td>ICH</td>
<td>Intracerebral haemorrhage</td>
</tr>
<tr>
<td>i.v.</td>
<td>Intravenous</td>
</tr>
<tr>
<td>LA</td>
<td>Local anaesthesia</td>
</tr>
<tr>
<td>L-dopa</td>
<td>Levodopa</td>
</tr>
<tr>
<td>MER</td>
<td>Micro-electrode recording</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>MS</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>PC</td>
<td>Posterior commissure</td>
</tr>
<tr>
<td>PEV</td>
<td>Pulse effective voltage</td>
</tr>
<tr>
<td>PD</td>
<td>Parkinson’s disease</td>
</tr>
<tr>
<td>PPS</td>
<td>Pulses per second</td>
</tr>
<tr>
<td>PVP</td>
<td>Postero-ventral pallidotomy</td>
</tr>
<tr>
<td>PW</td>
<td>Pulse-width</td>
</tr>
<tr>
<td>RF</td>
<td>Radiofrequency</td>
</tr>
<tr>
<td>SE</td>
<td>Schwab and England scale</td>
</tr>
<tr>
<td>STN</td>
<td>Nucleus Subthalamicus</td>
</tr>
<tr>
<td>SN</td>
<td>Substantia Nigra</td>
</tr>
<tr>
<td>SNR</td>
<td>Substantia Nigra reticularata</td>
</tr>
<tr>
<td>UPDRS</td>
<td>Unified Parkinson’s disease rating scale</td>
</tr>
<tr>
<td>V</td>
<td>Voltage</td>
</tr>
<tr>
<td>Vim</td>
<td>Nucleus Ventralis Intermedius thalami</td>
</tr>
<tr>
<td>VPM</td>
<td>Nucleus Ventroposteromedialis thalami</td>
</tr>
<tr>
<td>VPL</td>
<td>Nucleus Ventroposterolateralis thalami</td>
</tr>
<tr>
<td>CM</td>
<td>Centrum Medianum</td>
</tr>
<tr>
<td>X</td>
<td>Coordinate for laterality</td>
</tr>
<tr>
<td>Y</td>
<td>Coordinate for antero-posterior direction</td>
</tr>
<tr>
<td>Z</td>
<td>Coordinate for dorso-ventral direction</td>
</tr>
<tr>
<td>µs</td>
<td>Micro-second</td>
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HISTORICAL INTRODUCTION

As usual in the history of science, the history of stereotactic neurosurgery should not be considered as made up by a few isolated events, but viewed as a chain of numerous smaller or greater achievements and discoveries, all linked to the past, and sometimes also to the future. This short introduction is not intended to give an exhaustive analysis of the development of stereotactic neurosurgery for movement disorders, but rather to provide a sketch of the most important details in this chain of events, often with a somewhat simplified historical view.

The Renaissance period marked the end of medieval man and the dawn of the *homo nuovo*, and it seems appropriate to begin our history with its greatest son, Leonardo da Vinci, who might be said to be the link between the ancient schools of natural philosophy and modern science. Leonardo’s contribution to stereotactic surgery was small and probably without consequence for the future development, but it was none the less an interesting intellectual achievement. As a part of his general anatomical studies during the end of the 15th century, Leonardo became the first to produce a drawing of a skull divided by three intersecting reference planes, thus analysing the human skull and brain in a geometrical context\(^2\,208\).

Later, in 1543, Vesalius presented some images of sections through the human skull and brain in his anatomical work “De humani corporis fabrica”. During the same century, horizontal views of the brain were presented by Ambroise Paré, while George Bartish published an atlas of the human brain\(^207\). The work of Descartes in the 17th century was notable in that it provided a method of identifying any given point in space in relation to three intersecting planes at right angles, according to the Cartesian coordinate system, which is the foundation of the stereotactic method\(^2,41,113\).
The development continued during the following centuries, and observers in the 19th century could witness major progress concerning knowledge and mapping of the brain, in accordance with the general development in the field of anatomy and physiology, including the first attempts at stereotactic neurosurgery.

The recent renaissance of stereotactic functional neurosurgery has not just resulted in an increased interest for its future, but also for its past, as seen by the increasing number of papers on the history of stereotaxy. One of the most debated questions concerning the history of stereotaxy is the relative contribution of different scientists to the development of the stereotactic frame.

In efforts to trace the ancestry of stereotactic neurosurgery as far back as possible, many authors start their history as early as 1873, with the work of Carl Dittmar (1844 – 1920). His work is often seen as the first historical sign of a development leading to the stereotactic frame. Since modern recounts of the work of Dittmar seem to be sometimes inconsistent, his contributions will be dealt with in some more detail, than the topic might deserve.

The Institute of Physiology opened by Professor Carl Ludwig in Leipzig in 1869 was probably the most advanced experimental laboratory in the world at the time. Carl Ludwig was one of the prominent figures in early modern physiology based on natural science as opposed to natural philosophy, and his influence concerning many aspects of physiology can hardly be overestimated. Ludwig’s experiments led him to suggest that contractions of the arterial blood vessels were controlled by a vasomotor center in the medulla oblongata. These studies were continued by Owjannikow in 1870, who performed incisions by free hand in the medulla oblongata during continuous blood pressure measurement in order to define the extent of the vasomotor center.
were continued by Dittmar, who performed his studies at the Institute in Lepzig during 1870 –
1873\textsuperscript{22}. In his own contribution to refine the methods of these experiments, Dittmar had
invented a device which he presented in his article “Über die Lage des sogenannten
Gefaesszentrums in der Medulla oblongata”\textsuperscript{65}, published in 1873 in “Berichte über die
Verhandlungen der Königlich-Sächsischen Gesellschaft der Wissenschaften zu Leipzig,
mathematisch-physische klasse”. The purpose of this device was to eliminate unnecessary
movements of the rabbit’s head and of the operator’s free hand, in order to place the incisions
with higher accuracy. The apparatus also provided the possibility of controlling the depth of
the incision, and to allow reinsertion of the knife in defined spatial relations to the former
incisions. The apparatus was fastened to the snout of the rabbit. After the brain had been
exposed, the point of the incision was chosen visually and the blade was introduced under
direct visual guidance.

The impression provided by the modern literature differs slightly from this in
that most publications claim that Dittmar used his device for introduction of electrodes.
Further, the literature is in agreement, when this is specified, that the apparatus was
constructed for use in rats and that the experiments were performed on these animals.

It seems possible that the non-existing electrodes might have been introduced
into the historical discussion through a misinterpretation of a passage in Gillingham’s
“Stereotactic surgery--past, present, and future” from 1965\textsuperscript{99}:

“\textit{As long ago as 1873, in pursuit of the definition of fiber tracts and their functions, small
localized lesions were made in the brain of the rat by Dittmar\textsuperscript{65} in Ludwig’s physiological
laboratory, using a small knife attached to a simple guiding apparatus. From that time
onward, cerebral and spinal function in animals was investigated in this way, with
increasingly accurate methods, using localized low voltage electrical stimulation and
destructive lesions, and much later by depth microelectrode recording.}”
The hypothetical rat of Dittmar probably also owes its introduction to the historical discussion of Gillingham’s article, since it was mentioned here for the first time.

Dittmar’s apparatus has been called a guiding device, a technique for the spatial localization of intracranial structures or localization of specific points in the brain, etc. However, Dittmar’s device was constructed to allow a steadier way of performing incisions in the medulla oblongata, an improvement from those that were performed by free hand. The point of the incision was chosen visually, and the blade was introduced into this point under direct visual guidance. The apparatus should therefore, in my opinion, most properly be described as a supportive arm.

The first “pre-stereotactic” frame for use in humans was presented by Zernov in 1889. This “encephalometer” was fixed to the skull with rests placed in a standardized manner according to the position of the superior margins of the orbits, the external auditory meatuses, the nasion, and a fifth over the sagittal suture in the parietal region. Zernov also created a statistical atlas of the surface structures of the brain, which was used with the encephalometer in a polar coordinate system. Later, in collaboration with his adept Altukhov, he made a map of the basal ganglia. These maps were based on external landmarks of the cranium, which led to a high degree of inaccuracy due to the high degree of variability in the anatomy of the human skull. The encephalometer could be used for identification of surface structures underlying a given point of the skull on the atlas, or vice versa, the position of a structure could be indicated on the skull with the help of the atlas. This frame is reported to have been in frequent clinical use, for example in the identification of abscesses. A successor of the encephalometer, the “brain-topograph” was later constructed by Rossolimo. Neither of these Russian frames were based on Cartesian coordinates, and therefore they were not fully stereotactic.
An early French frame from 1897, developed for localization of intracranial projectiles, has recently been presented by Benabid \(^{17,236}\). The frame was mounted on the head of the patient with two Crookes tubes and two supports for film attached to its sides, thus producing X-rays in two projections. The frame is reported to have been used successfully in two cases. Even though this seems to have been a truly stereotactic construction, knowledge of this frame apparently did not spread and contribute to further technical development.

What has generally been considered to be the first stereotactic frame was presented in 1908 by Victor Horsley and Robert Henry Clark\(^{130}\). The Horsley-Clarke frame was applied to the skull using rods with plugs inserted into each external meatus and bars resting on the lower orbital rims and the nose. One of the major achievements was that Clarke decided not to relate the target to external structures, but rather to three internal planes. The horizontal plane stretches from the center of the auditory meatus to the inferior orbital border. The frontal plane is orientated at a perpendicular angle to the horizontal plane and the sagittal plane is perpendicular to the other planes and divides the hemispheres. Based on these planes, stereotactic atlases were constructed for cat and monkey, demonstrating sections of the brain in relation to external landmarks\(^{92,130,145,256}\).

The first model of the frame only permitted movements of the electrode in the three perpendicular planes, but this weakness was overcome in a later version of the frame with an “equatorial system”\(^{80,113,234}\). Several copies of the Horsley-Clarke frame, with different modifications, were later constructed by other researchers\(^{80}\).

Clarke realized the possibilities of the stereotactic method, and patented the idea of a stereotactic frame for use in humans, suggesting that it might be used to treat brain tumours “by electrical means or by the placement of radium, relief of pain by coagulation of intracerebral tracts, and direct application of drugs and pharmaceuticals into the CNS”\(^{43,92,144}\).
The idea of a stereotactic frame for humans was however not realised by Clarke, but by Mussen, a co-worker of Horsley and Clarke, who later designed a stereotactic frame based on the Horsley-Clark frame for use in humans around 1918. This frame was however never actually used, and did not contribute to future frame development. In 1933 Kirschner presented a stereotactic device for electrocoagulation of the trigeminal ganglion via the foramen ovale in the treatment of Trigeminal neuralgia. The identification of the target was based on external landmarks.

The first stereotactic frame to be used in human, and the starting-point of stereotactic neurosurgery, is generally considered to be the frame of Spiegel and Wycis, presented in 1947. Spiegel had previously been working with the Horsley-Clarke frame in animal experiments, and the new frame demonstrated a close resemblance to the predecessor. A major achievement was that the first stereotactic atlas of the human brain by Spiegel and Wycis was based on internal landmarks which were identified during surgery with pneumoencephalography, a method introduced by Dandy in 1918. The reference points initially used were the foramina of Monro (FM), the anterior commissure (AC), and the calcified pineal. Due to variability in the position of the pineal calcification, this was later suggested by Talairach to be replaced by the posterior commissure (PC). Since then, the AC-PC plane has remained the standard reference plane in functional stereotactic neurosurgery.

The impetus for the development of Spiegel-Wycis frame had been the staggering side-effects of the prefrontal lobotomy. Dissatisfied by the frequent complications of this method, Spiegel and Wycis considered the stereotactic method to be a less extensive alternative. The first stereotactic procedure presented in man was therefore dorsomedial thalamotomy performed as an alternative treatment for lobotomy. Spiegel and Wycis had also performed pallidal lesions for movement disorders, pain procedures, electrocoagulation of the
Gasserian ganglion, as well as drainage of cystic tumors, when they reported their first psychosurgical operations\textsuperscript{95,194,273,274}.

The work of Spiegel and Wycis rapidly attracted attention, and a number of different stereotactic frames were developed by Leksell, Talairach and many others\textsuperscript{10,11,27,46,48,107,142,174,186,209,233,243,245,287,293,309} at the same time while new atlases were presented by Talairach, Schaltenbrand and Bailey, and others\textsuperscript{7,208,253,254,281,286,299}.

The history of neurosurgery for movement disorders, however, had started a long time before the introduction of the stereotactic technique. Open procedures for movement disorders were performed as early as 1909 by Horsley, who removed a part of the motor cortex in order to treat hemi-athetosis. The operation resulted in a hemi-paresis, but the patient’s previous symptoms were abolished\textsuperscript{129,227} Later, cortical excision of Areas 4 and 6 was reported by Bucy to relieve tremor, but hemiparesis and an operative mortality of over 10\% did not contribute to the procedure’s popularity\textsuperscript{38-40,85,234}. Other open procedures with lesioning of the pyramidal tract were also tried, but were met with limited success\textsuperscript{36,106,193,234}.

Operations in the basal ganglia had been a surgical \textit{noli me tangere}, since Dandy asserted that the basal ganglia was a part of the center of consciousness\textsuperscript{57,85,192}. The first to operate on the basal ganglia was Meyers, who in 1941 achieved tremor reduction without paresis using a transventricular approach and resection of the head of the nucleus caudatus, anterior limb of the internal capsule and cutting of the ansa lenticularis. Even though the results were favourable concerning the Parkinsonian symptoms, the mortality rate was 12\%\textsuperscript{108,192,227,234,281}. Mortality rates of up to 41\% were reported by others performing this procedure\textsuperscript{36,108,109}, thus making it an unacceptable alternative. During the fifties, a sub-frontal approach to the ansa lenticularis was developed by Fenelon, and Guiot and Brion used the same approach to the Globus pallidus internus (Gpi)\textsuperscript{77,105,108}.
Unintended ligation of the anterior choroidal artery during an attempted pedunculotomy, with probable ischemic lesions in the medial globus pallidum, ansa and fasciculus lenticularis and the ventrolateral thalamic nucleus by Cooper in 1952, resulted in decreased tremor and rigidity in a parkinsonian patient. This procedure was therefore evaluated in a group of patients, but the results were varying and the mortality was 10%\textsuperscript{49,227,281}.

The introduction of the stereotactic technique by Spiegel and Wycis presented tremendous possibilities concerning minimal invasive neurosurgical treatment of movement disorders. Even though their first publications described medial thalamotomies for psychiatric disease, the first operation they performed in 1946 was a pallidotomy in a patient with Huntington’s chorea\textsuperscript{96,275}. Pallidotomies soon became the treatment of choice for Parkinson’s disease (PD), and Spiegel et al. reported an operative mortality for pallidotomy of 2%, while Reichert reported even lower mortality rates\textsuperscript{234,244,276}.

During this period the main goal in the treatment of Parkinson’s disease was to alleviate tremor, and after the first ventrolateral (VL) thalamotomy had been performed by Hassler et al. in 1954, the method soon surpassed pallidotomy in popularity, due to the superior effect on tremor\textsuperscript{28,34,96,120,121,164,234,244}.

Other targets than the pallidum and the thalamus were also explored in the treatment of different movement disorders. The reports of the procedures performed during this period often were not as detailed as might be wished. The exact localisation of a lesion was seldom known, since the only way of determining this was to perform an autopsy. The lesions also varied in size and not seldom did a lesion involve more than one area. Furthermore, the terminology in the reports was not always clear, and even if the procedures were given the same name, the intended target often varied substantially between different surgeons, as demonstrated in an article by Laitinen\textsuperscript{172}.
One of the most popular targets besides the pallidum and the thalamus was the subthalamic region. It is important to realise that even though subthalamotomies today most often signify lesions performed in the nucleus Subthalamicus (STN)\(^4,5,98,179,282,283\), this has only been the case since the introduction of deep brain stimulation (DBS) in this target. Prior to this, lesions were never performed intentionally in the nucleus Subthalamicus, even though the nucleus might have been involuntarily lesioned as a part of procedures performed in the area\(^71\). Subthalamotomy does here signify lesions in the subthalamic area that might include the Zona incerta, the prelemniscal radiation and the prerubral area\(^8,25,26,71,128,162,163,172,195,197,199-201\). Lesions performed in the field of Forel might also be included under the name of subthalamotomy, but often these lesions were specified as campotomies\(^278,279,306\).

The first lesions performed in humans were made with electrolytic direct current, but other methods were later developed, such as injections of procaine-oil or coagulating substances, and lesions performed with cryoprobe, leucotome and radiofrequency (RF) electrodes\(^46,50,92,202,205,206,211,281\).

Stereotactic surgery, mainly for Parkinson’s disease proved to be a major success, and in 1965 more than 25,000 stereotactic procedures had been performed and in 1969 37,000 procedures\(^272,273\). The number of stereotactic functional procedures did however decrease dramatically after the introduction of L-dopa in 1968\(^108\).

After the introduction of the computed tomograph (CT)\(^134\) in 1973, advantages of this method, as compared to ventriculography, were quickly recognised. This readily feasible and non-invasive method contributed to widening the field of stereotactic neurosurgery and was important to spread the technology among neurosurgeons. The introduction of the CT did not only result in an increased interest in stereotactic non-functional neurosurgery, but also in a minor resurgence in stereotactic functional procedures\(^37\). The development of the magnetic resonance imaging (MRI) with its high
anatomic resolution made it possible to abandon targeting according to statistical coordinates for some targets, and to visually identify the area of interest. The development of computer software for 3-D image manipulation and calculation of coordinates have further contributed to the feasibility and popularity of the stereotactic technique.

The renaissance of the stereotactic functional neurosurgery practically commenced with the re-evaluation of Leksell’s posteroventral pallidotomy (PVP) in the treatment of Parkinson’s disease by Laitinen et al in 1992\textsuperscript{173}. After the initial success of L-dopa, new symptoms such as L-dopa induced dyskinesias and on-off phenomenon put a limit to the pharmacological treatment, which is why the promising results of Laitinen et al. resulted in a world-wide resurgence for pallidotomy in the treatment of Parkinson’s disease.

The second source of this renaissance was the introduction of deep brain stimulation by Benabid et al\textsuperscript{21}. Intra-operative macrostimulation had been used for target localization since the birth of stereotactic functional neurosurgery in 1947, and it had been noted that while low-frequency stimulation could enhance tremor and other symptoms, high-frequency stimulation resulted in a reduction of symptoms\textsuperscript{120,121,136,149,178,251,265,277}.

The next step forward from intra-operative macrostimulation was taken with implantation of externalised electrodes for testing outside the operation ward, as well as for lesioning. During the sixties, Sem-Jacobsen\textsuperscript{261-263} advocated implantation of multiple electrodes, and used these to identify the optimal lesioning site during weeks or months of test stimulation in patients with Parkinson’s disease. If a satisfying effect was not achieved further lesions could be made at a later stage via the implanted electrodes. The technique with implanted electrodes and repeated micro-lesions, was also used by Van Buren\textsuperscript{298} at this time.

The first one to use stimulation as a therapy was however Bechtereva\textsuperscript{13}. In the early 70’s her group treated various conditions, including Parkinson’s disease and dystonia, with stimulation of the thalamus and basal ganglia. During surgery 20-40 electrodes in 5-6
bundles were implanted into the deep structures of the brain. The patients were thereafter treated with intermittent courses of stimulation for up to 1.5 years. Beneficial results were reported also under the stimulation-free periods.

Implantable RF-stimulators had been invented already in the early 30’s, and were used for stimulation of the phrenic nerve for artificial respiration as early as 1963\cite{42,59,100}. The first battery-powered cardiac pacemaker was implanted in 1960, and this led to the development and implantation of the first battery-powered neuro-pacemaker in 1976\cite{59}. With the development of implantable systems for electrical stimulation, DBS soon became an accepted treatment for certain types of pain\cite{96,131,132,241,242}. The implantable systems did also lead to an increased interest in the possibilities of DBS in the treatment of movement disorders. Cooper\cite{51-53} started with chronic stimulation of the cerebellar cortex for cerebral palsy in 1972. The observation that the thalamic somatosensory response was depressed by cerebellar stimulation, and that the stimulation demonstrated effects similar to thalamotomy, later led to direct stimulation in the thalamus and the internal capsule. DBS was tested for various conditions, including dystonia, torticollis, multiple sclerosis (MS) and spasticity, with rather good results.

After initially having used implantable DBS systems for the treatment of pain, Mundinger\cite{196,198} implanted in 1975 a patient with torticollis with a DBS system in the motor thalamus, pulvinar and dentate nucleus. DBS was later used also for athetosis, dystonia and spasticity, and the outcome was reported to be good. In 1980 Brice and McLellan\cite{35} presented good results from permanently implanted DBS-electrodes in the subthalamic area in two patients with MS-tremor. In the same year Mazars et al demonstrated beneficial results of intermittent stimulation in the nucleus ventroposterolateralis thalami (VPL) on dyskinesias secondary to sensory deafferentation. This encouraged them to try intermittent stimulation in the VL in patients with Parkinson’s disease and action tremor, which however met with little
success. The positive results in the VPL were later reproduced by Siegfried\textsuperscript{266} in 1986. In 1983 Andy presented good results from intermittent DBS in various parts of the thalamus, including the nucleus ventralis intermedius thalami (Vim), in the treatment of PD, tremor of other origin and torticollis.

It was however not until after the publication of Benavid\textsuperscript{21} in 1987 concerning DBS in the Vim in the treatment of tremor that the method started to be considered as a therapeutic alternative. The introduction of the Subthalamic nucleus as a target for DBS in the treatment Parkinson’s disease in 1993 by the same group\textsuperscript{231} and the application of DBS on the Gpi by Siegfried et al\textsuperscript{267,268} have further contributed to the rapidly growing interest in this field. DBS in various nuclei of the basal ganglia and thalamus is now an established treatment for various movement disorders and the number of patients with implanted devices is estimated to more than 25,000\textsuperscript{54}. 
BACKGROUND OF THE PRESENT STUDY

*Primum est non nocere* should always be the first concern for any treatment. When abstaining from treatment would be likely to result in severe morbidity or death, such as for example in aneurysmal subarachnoid haemorrhage, the risk of surgery has to be weighted against the anticipated benefit of the operation, why a rather high surgical morbidity/mortality can be justified in these cases. Stereotactic functional neurosurgery in the treatment of movement disorders is however not performed on vital indication, nor is it a curative treatment. It is aimed at reducing symptoms and increasing the patient’s quality of life, which is especially evident concerning benign conditions such as essential tremor (ET). These conditions will untreated not reduce the life-expectancy of the patient, nor lead to development of other diseases. When treating such a condition the equation of risk and benefit will clearly differ substantially from surgery on vital indication, and only treatments with a very low risk of serious complications can be accepted.

In order to perform an adequate risk to benefit analysis for the different available treatments it is of importance not only to know the efficacy of the treatment, but also to know the rate and nature of possible complications. Concerning lesional surgery much of the published material consists of rather old studies, most often performed without adequate scales, which makes it difficult to form a grounded opinion of the efficacy of the treatment. Further, the data concerning complications is often poorly presented, and sometimes raises the question of whether this aspect of the material has been thoroughly scrutinized. Concerning DBS, most studies are for apparent reason of a rather modern date, and the acute effects and side effects of DBS in the treatment of movement disorders are fairly well studied. DBS is however a life-long treatment with implanted foreign materials under constant risks of
causing or suffering injury, while the published experience concerning the long-term results is limited.

The work with this thesis was undertaken in order to analyze our own experience of stereotactic functional procedures with special emphasis on complications and safety. Since these aspects of the material will tend to dominate the material, some words must be said concerning the terminology:

Concerning the terms *complication* and *side effect* there seems to be different opinions in the society on the exact definition of these words, and on how they differs in denotation. I have had the impression that *complication* sometimes seems to imply a more severe unwanted and unexpected effect of a treatment, while *side effect* at times seems to be used to imply less severe, and sometimes anticipated effects of the treatment.

If one were to apply these criteria to stereotactic functional neurosurgery for movement disorders it seems likely that *complication* might be more appropriate for unwanted effects such as haemorrhages, ischemia, infections of implanted materials etc, while *side effect* seems more appropriate for phenomenons such as stimulation induced paresthesias, rebound phenomenon etc.

Such a distinction between these two terms might seem convenient, but is non the less false. No support for such a distinction is to be found in dictionaries of the English language, nor in medical dictionaries. Nor, according to my personal opinion, does a clear distinction exist in the general usage of these terms in the modern scientific literature. Even though a tendency might sometimes bee seen in the literature in accordance with the above mentioned, it is my impression that the terms are most often used interchangeably as synonyms.
The etymological literature is extensive and the purpose of this thesis is not to investigate the exact definition of these terms, their origin or their evolution over time, but a few words might be said to avoid any misconceptions. Since no differences of importance seems to exist between different dictionaries the quotations used here has been limited to the Oxford English Dictionary.

While the components of side effect can be traced back to the common Teutonic and ancient Latin, respectively, the combination of these two words is of a rather modern origin. The term side effect (also: side-effect) is first recorded in 1884. The general meaning is “A subsidiary consequence of an action, occurrence, or state of affairs; an unintended secondary result”. The word was later to be used in the field of medicine with the meaning “An effect (usu. for the worse) of a drug or other chemical other than that for which it is administered”. This meaning is recorded from 1939. The term was later also used in connection with surgical therapies. It should be noted that even though the term is usually used for negative effects other than the intended, it might also be used for positive or neutral effects other than the intended. The terms adverse effect and adverse event are more specific and might be defined as a negative side effect.

Concerning complication the simplest definition is “Something that complicates or adds difficulties; a complicating factor”. The term has been used in a medical context since the 17th century, initially with the meaning “an additional disorder or condition that develops during the course of an existing one”, and later also concerning things that complicates the situation and are caused by a therapy.

In conclusion, there is no support for differentiating between the terms of side effect and complication. These words are synonymous, except for that side effect might be, but seldom is, used not only for negative effects, but also for effects of a positive or neutral nature.
other than the intended, while *complication* only can be used for not intended effects that complicates the situation, that is, negative effects.

Languages are in a constant state of evolution, and even though there is no support today for differentiating between these two terms, the tendencies I believe to have noticed towards such a development might reflect a need, and might in the future create a clear difference in denotation. To avoid confusion it would be of value to the medical society to clearly define the meaning of these terms.

In this thesis the terms will be used in accordance with their present meaning, and can thus be regarded as interchangeable.

The background of each paper will be presented in some detail below.

**Paper I**

After the introduction of DBS in the Vim for Parkinsonian tremor in 1987, and for essential tremor in 1991, it has been demonstrated that Vim-DBS is preferable to thalamotomy concerning complications, while the efficiency is equal or superior. The re-introduction of posteroventral pallidotomy in 1992 by Laitinen et al resulted in a worldwide interest in this procedure, but the application of DBS on the Gpi, and the introduction of STN as a new target for DBS in the treatment of Parkinson’s disease, have however resulted in a decreased interest in pallidotomy. DBS has thus today become the treatment of choice and is increasing rapidly, while lesional surgery (thalamotomy and pallidotomy) has declined proportionally.

In surgery for movement disorders, it has been claimed that ablative lesions carry a higher risk of complications, compared to DBS, and the major arguments for DBS have been its safety and reversibility. While it is obvious that DBS has certain
advantages compared with lesioning \cite{223,257,288,289}, it does however also carry some disadvantages: DBS is considerably more expensive and more laborious than lesional surgery, necessitating repeated follow-up with multiple optimizations of stimulation parameters. DBS does also carry the risk of hardware-related complications \cite{23,31,146,157,213,295}. Taking into account these disadvantages with DBS, it is of importance that the relative risk of the different methods, as well as their efficacy, should be thoroughly evaluated, before lesional surgery is completely abandoned in favour of DBS\cite{216}.

The published material which allows a comparison between the two methods is scarce. We have therefore in this study performed a general analysis of our material from the last twelve years in lesional surgery versus DBS in the treatment of movement disorders, with respect to the occurrence of adverse events.

**Paper II**

The major difference between lesioning and DBS is that the later is based on implanted foreign materials requiring life-long follow-up. While the effect of a lesion seldom changes dramatically in the short term, the opposite is true of DBS since the effect of the treatment is dependent on the continuous function of these implants. Patients with DBS are often highly dependent on their treatment for their well-being, and malfunctioning of the system can result in acute severe debilitating symptoms or severe disabilities \cite{117}.

Only a few systematic studies of hardware-related complications of DBS have however been presented \cite{23,146,157,213}, and only one study has provided a follow-up and risk prediction in term of electrode-years \cite{146}. In order to thoroughly evaluate the risks-to-benefit of the method it is important to investigate the hardware-related complications over a longer period. The aim of this study was to thoroughly analyse the hardware-related complications
encountered in our consecutive series of patients treated over a period of ten years. Further, to suggest how the risk for these complications can be minimized.

**Paper III**

A special form of hardware-related complications is constituted by electromagnetic environmental influences, a topic which previously has received very little attention. Many of the patients operated on with DBS for movement disorders gain an increased mobility from this treatment, and return to a relatively normal lifestyle in the community. However, today there is a steadily increasing number of electromagnetic devices in our modern daily environment which might have the potential to interfere with these neurostimulation devices. Furthermore, many patients with DBS are older adults, and may have or may develop coexisting diseases requiring medical treatments or diagnostic studies that involve some form of electromagnetic field generation. Issues such as compatibility and safety between the DBS system and MRI, ECG, cardioversion, diathermy and other devices create insecurities for patients and caregivers and may be potentially harmful to patients. The issue of MRI and DBS has been discussed in a number of publications\(^{29,89,143,237-240,280,292,294}\). However, even though some reports have been published concerning hard-ware related complications in general\(^{23,31,110,157,184,213,258}\), only a few case-reports dealing with isolated cases of external influences has been presented\(^{187,210,212,249,280,300,307}\). The objective of this study was to report our experience with respect to all forms of external electromagnetic influences on DBS, how these electromagnetic influences affected our patients’ daily lives and other various healthcare-related situations. Furthermore, the study aimed to identify suggestions for how some of these electromagnetic influences might be managed in order to minimize risks and inconveniences to the patient.
**Paper IV**

Several publications have reported that depression may occur after STN-DBS \(24,66,133,188,246,290,301,305\). This has often been attributed to the marked reduction of L-DOPA postoperatively \(16,159,305\), and not to a direct effect of STN stimulation. It does however seem as if acute stimulation itself in this area can cause certain psychiatric side effects. Bejjani et al. have reported a patient in whom stimulation of the left-sided substantia nigra reticulata (SNR) just ventral to the STN gave rise to acute stimulation-induced depression \(^{15}\). In this paper we present a patient in whom intra-operative macrostimulation in the right-sided area ventral to the STN provoked an acute depression.

**Paper V**

Both posteroventral pallidotomy \(^3,55,60,62-64,74,90,137,170,173,284\) and pallidal DBS \(^14,67,87,175,177,267,268,305\) have a documented effect on parkinsonian symptoms, but the relative effectiveness of these methods has rarely been evaluated \(^{190}\). It has not been demonstrated in the literature that unilateral pallidal DBS is superior to pallidotomy, neither concerning risks, nor concerning efficacy.

The aim of this study was to analyse the long-term effect of each surgical procedure, pallidotomy and pallidal DBS, on contralateral symptoms in the same patients.

**Paper VI**

The results of thalamotomy in the treatment of tremor are favourable, both concerning the acute effects \(^{47,101,102,141,171,215}\) and the long-time results \(^{204,214}\). It has however been demonstrated that the complications of Vim-DBS are milder or less frequent than for thalamotomy, while the efficiency is equal or superior \(^{30,223,257,288,289}\). Vim-DBS is now established and constitutes the surgical treatment of choice for essential
tremor\textsuperscript{20,33,119,155,176,223,257,288,289}, and its short term effects are well documented. Even though the method was introduced almost two decades ago, there is however very little published experience concerning the long-term efficacy of Vim-DBS\textsuperscript{156,222,232,235,285}. The aim of this study was to prospectively analyse the long-term effect of Vim-DBS in a group of patients with ET.
AIMS

The specific aims of this thesis were:

- To evaluate complications in stereotactic functional neurosurgery for movement disorders, concerning both lesional surgery and deep brain stimulation, for procedures in the STN, pallidum and Vim.
- To analyze in detail complications related to implanted materials during DBS, and how these might be reduced.
- To investigate in a clinical material how external electromagnetic forces might affect implanted DBS systems, and how potential risks associated with this interference might be minimized.
- To compare the effects and side effects of pallidotomy and pallidal DBS in the treatment of Parkinson’s disease.
- To evaluate the long-term efficacy of Vim-DBS in the treatment of essential tremor.
MATERIALS AND METHODS

Paper I
This is a retrospective study of 197 consecutive patients undergoing treatment at the department of Neurosurgery, University Hospital of Umeå, during the period 1990 – 2002 with stereotactic surgery for Parkinson’s disease and various forms of tremor. Records of the patients were retrospectively analysed with respect to demographic data, diagnosis, surgical technique and complications.

Paper II
This is a retrospective study of 139 operations performed in 119 consecutive patients treated at the department of Neurosurgery, University Hospital of Umeå, with DBS for movement disorders and pain during the period 1993 – 2002. Records of the patients were analysed with respect to demographic data, diagnosis, surgical technique and complications.

Paper III
This is a retrospective study of 172 patients operated with DBS for movement disorders. Of these patients 110 were operated at the department of Neurosurgery, Umeå University Hospital, Umeå, Sweden and 62 at the Parkinson and Movement Disorders Centre, Byblos, Lebanon. All patients in the present study were treated for movement disorders (Parkinson’s disease, tremor of various origins, and dystonia) with chronic DBS in either the subthalamic nucleus, posteroverentral pallidum or nucleus ventralis intermedius of the thalamus. The medical records of the patients were retrospectively analysed with respect to events related to external electromagnetic influences on the DBS system.
Paper IV

This is a case report presenting a 62 years old male patient with Parkinson’s disease, in whom intra-operative macrostimulation in the right-sided area ventral to the STN provoked an acute depression.

Paper V

This is a study of five consecutive patients, two women and three men, who underwent unilateral pallidotomy, followed in a later session by contralateral pallidal DBS. All patients had bilateral on-off phenomena, bradykinesia, rigidity and dyskinesias. Three patients had also tremor. The initial pallidotomy was performed contralateral to the most affected side of the body. All operations were performed by the same surgeon, at the department of Neurosurgery, University Hospital of Umeå.

The patients were assessed before surgery, and after the first and second operation according to the Unified Parkinson’s Disease Rating Scale (UPDRS)\textsuperscript{72}, Hoehn and Yahr (H&Y) staging \textsuperscript{72}, and the Schwab and England scale (S&E)\textsuperscript{72}. In order to distinguish the effect on the different sides, items no. 20-26 of the UPDRS III (tremor, rigidity, finger taps, hand grips, hand pronate/supinate, leg agility) and 32-35 of the UPDRS IV (dystonia and dyskinesias) were analyzed separately for each body side. The assessments were done before the initial pallidotomy, then before the pallidal DBS, and finally after the pallidal DBS. This final assessment was performed at a mean of 37 months (range 22-60) after the pallidotomy, and 22 months (range 12-33) after the pallidal DBS. At the final assessment, the evaluator was blinded as to which body side was contralateral to pallidal DBS and which was contralateral to pallidotomy. At this evaluation, the DBS was not switched off and the assessments were performed during the patient’s best “on” and worst “off” states\textsuperscript{112}.
Paper VI

In a previous publication, a group of 27 consecutive patients treated with Vim-DBS for essential tremor were presented after a mean follow-up of one year\textsuperscript{111}. These patients have now been re-evaluated for a long-term follow-up.

Of the original 27 patients, 4 died during the follow-up period of causes not related to surgery. In two patients the diagnosis has been revised during the follow-up period from essential tremor to dystonic tremor, and in one patient to cerebellar tremor. These patients have therefore been excluded. One patient was lost to follow-up, since her medical condition was too poor to allow her to travel to the hospital for evaluation. Thus, findings from 19 patients with long-time follow-up have been analysed.

Previous surgery included two ipsilateral and one contralateral thalamotomy and one contralateral Vim-DBS. Eighteen of the patients were operated on the left side. All procedures were performed by the same surgeon, at the department of Neurosurgery, University Hospital of Umeå, between 1996-1999\textsuperscript{31}.

The patients were evaluated according to the essential tremor rating scale\textsuperscript{73} (ETRS) 1 to 3 days before surgery, and ‘on and off’ stimulation at the initial follow up after a mean of $13 \pm 4.9$ (SD) months (range 6 - 26). A final evaluation was done after $86 \pm 9.0$ (SD) months (range 66 – 102) after surgery. During the post-operative evaluations, neither patient nor evaluator had access to the results of the previous evaluations. The evaluation has been described in detail previously\textsuperscript{111}. 
Surgical Technique

The Laitinen stereotactic system\textsuperscript{115} was used in all patients in papers IV, V, VI, and in all but seven cases in papers I and II. The last seven procedures were performed with the Leksell system\textsuperscript{181}. In papers I, II, IV, V and VI identification and calculation of target coordinates was performed on enlarged hard copies of CT / MRI films\textsuperscript{127}.

The target in the Vim was identified with stereotactic CT-studies\textsuperscript{127}, and chosen 13-15 mm lateral to the midline of the 3\textsuperscript{rd} ventricle, at the level of the intercommissural line, and 6-7 mm anterior to the posterior commissure. The pallidal target was identified with stereotactic MRI-studies, and visually chosen 2 mm anterior to the mid-commissural point, 2 – 3 mm lateral of the pallido-capsular border on the axial slices, and about 2 mm above the optic tract on the coronal slices. The target in the STN was visually identified on MRI-studies, and chosen at the line connecting the anterior borders of the Ruber nuclei, at the level of their maximal diameter, and approximately 1.5 mm lateral to the medial border of the STN. The depth was when needed corrected according to the lower border of the STN as seen on the coronal slices.

All patients undergoing DBS, and 36.7\% of patients in paper I undergoing lesions, received prophylactic treatment with i.v. antibiotics, normally one dose of Cefuroxim 1.5 gram in lesion-patients and three doses a day for three days in DBS-patients.

The whole head was shaved prior to DBS, while only partial shaving was performed for lesion-patients. The patient was placed in a semi-sitting position on the operation table, in order to minimize leakage of cerebrospinal fluid (CSF). Lesioning and electrode implantation were performed under local anaesthesia. For lesional surgery, a linear incision of approximately four centimetres was placed centred over the place for the burr-hole. For DBS small skin-flaps were opened. A burr-hole of 8 mm in diameter was used in
lesions and in the early cases with DBS, when the electrode was sutured to the skull, and in the later cases with DBS a burr-hole of 14 mm. The burr-hole was performed with a hand-drill, and placed just anterior to the coronal suture and approximately 2.5 – 4 cm lateral of the midline, depending on the target. Durotomy and corticotomy were performed with monopolar coagulation.

Normally a RF-electrode with a 1.8 x 2 mm non-insulated tip was used for impedance measurement, track making, intraoperative stimulation, and lesioning. The lesions were normally produced with a temperature of 75 – 80 ºC during 60 s for pallidotomies and 70 - 75 ºC for thalamotomies. The pallidotomies were performed starting 6 mm above the most ventral target level, with one lesion every two mm, provided that macrostimulation did not yield capsular or visual response. The thalamotomies were normally performed at two levels separated by two mm.

If DBS was intended, the RF electrode was used for impedance measurement and track making after which it was replaced with the Medtronic DBS electrode 3387® or 3389® (Medtronic, Minneapolis, MN, USA) for macro-stimulation.

The effect of intraoperative stimulation on symptoms such as tremor, rigidity, hypokinesia, and eventual induction of dyskinesias was evaluated and possible side effects, such as visual phenomena, capsular response, speech alterations and paresthesias were sought. In all patients, surgery was performed without microelectrode recording. If the stimulation effect was difficult to assess intraoperatively, the electrode was in a few cases externalised for further testing in the ward.

In the initial cases of DBS, the DBS-electrode was anchored to the burr-hole using silicon tube and suture and the connection between electrode and cable was placed below the mastoid. In the subsequent cases the Medtronic burr-hole cap® (Medtronic,
Minneapolis, MN, USA) was used and the connection placed on the calvarium, in the vicinity of the burr-hole.

Implantation of the IPG (Itrel II®, Soletra® or Kinetra®, Medtronic, Minneapolis, MN, USA) and connection cables was in most cases performed in the same session as the electrode implantation, but normally under general anaesthesia. The neurostimulator was placed in a subcutaneous pocket below the clavicle.
STATISTICS

Paper I-III
Results are reported as means, range and percent. In paper II the Kaplan-Meier survival plot was used in the description of the material.

Paper V
The non-parametric Wilcoxon signed rank test was used for statistical comparison between pre-operative and post-operative scores for each method. The Mann Whitney U test was used for comparison between the methods. $P \leq 0.05$ was considered as statistically significant.

Paper VI
Results are presented as mean $\pm$ SD and range. ANOVA for repeated measurements was used for calculation of significant differences for continuous variables and the Bonferroni test was used as post hoc test. The non-parametric Friedman’s test was employed for discrete variables and followed by Wilcoxon’s signed rank test as post hoc test. The latter test was also used when comparing only two non-parametric values. A p-value $\leq 0.05$ was considered statistically significant.
RESULTS

Paper I

The 197 patients underwent 127 procedures with lesions or attempted lesions and 129 DBS, with implantation of 151 electrodes. One hundred lesions were performed for Parkinson’s disease and 25 for Essential tremor. For DBS the figures were 69 and 49, respectively. The number of procedures according to brain target is presented in table 1. With exception of one patient with cardiovascular disease, who died in a heart-attack one month after a thalamomy, the mean follow-up time was 40 months (range 6 - 144) after lesions, and 47 months (range 6 – 117) after DBS.

Table 1. Number of procedures according to brain target in Paper I and Paper II.

<table>
<thead>
<tr>
<th>Target</th>
<th>Paper I</th>
<th>Paper II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DBS</td>
<td>Lesion</td>
</tr>
<tr>
<td>STN-bilateral in one session</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>STN-left</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>STN-right</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>PVP-bilateral in one session</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>PVP-left</td>
<td>6</td>
<td>43**</td>
</tr>
<tr>
<td>PVP-right</td>
<td>3</td>
<td>33**</td>
</tr>
<tr>
<td>Vim-bilateral in one session</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Vim-left</td>
<td>69*</td>
<td>36</td>
</tr>
<tr>
<td>Vim-right</td>
<td>26*</td>
<td>15</td>
</tr>
<tr>
<td>VPM-VPL left</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VPM-VPL right</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CM left</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CM right</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>129</td>
<td>127</td>
</tr>
</tbody>
</table>

*Six of these patients underwent staged bilateral procedures.
** Twelve of these patients underwent staged bilateral procedures.

STN: Subthalamic nucleus; Gpi: Globus pallidus internus; Vim: Nucleus ventralis intermedius of thalamus; VPM-VPL: nuclei ventroposteromedial-ventroposterolateral of thalamus; CM: Centrum-medianum.
Seven of the lesional procedures and one DBS procedure were aborted before lesion / implantation due to malfunction of the equipment in two cases, haemostatic problems in one, and lack of positive response to macrostimulation and / or undesired side effects in five cases. In the remaining patients, a mean of 1.2 tracks (range 1-4) were used.

**Adverse events**

*Intracerebral haemorrhages (ICH):* One patient developed a subcortical haemorrhage after a pallidotomy. In one patient the arc of the stereotactic frame slipped while the RF-electrode was in the Vim prior to thalamotomy, and the operation was aborted when slight bleeding from the trajectory was noticed. One patient had a haemorrhage around the tip of the electrode after STN-DBS. All three patients were treated conservatively and recovered completely.

*Confusion and cognitive disturbance:* Seven patients with PD developed short-lasting confusion after lesioning. One pre-demented patient became severely demented\(^\text{118}\), and 2 other patients reported mild subjective deterioration of memory after bilateral STN-DBS. In 8 other patients with DBS, of which 7 had PD, confusion occurred.

*Psychiatric side effects:* Three patients with bilateral STN-DBS developed mild postoperative depression, which in one patient was preceded by a phase of euphoria.

*Paresis / gait-disturbance:* Twenty-eight patients (54.9%) with thalamotomy had dysequilibrium or disturbance of gait, which in 22 patients was still present four months after surgery. Three of the pallidotomy-patients had short-lasting weakness in the contralateral leg.

*Dysarthria and dysphonia:* Nine patients had dysarthrophonia secondary to lesion. This was permanent in four patients with thalamotomy and in one patient with pallidotomy. Two patients had transient dysarthria and one permanent hypophonia after unilateral pallidal-DBS, contralateral to a previous pallidotomy. Hypophonia occurred in four patients with bilateral STN-DBS.
Rebound and stimulation-induced side effects: Four cases of mild, seven moderate, and ten cases of severe rebound were seen after Vim-DBS. Two patients with STN-DBS had rebound symptoms\textsuperscript{119}.

In 16 patients with Vim-stimulation, some degree of stimulation induced dysarthria or affection of gait, had to be accepted in order to achieve an acceptable effect on the tremor. Eleven of these patients had undergone bilateral procedures.

Hardware-related complications and repeated surgery:

Hardware-related complications occurred in 13.2\% of the patients with DBS with a complication rate of 4.7\% per electrode-year. These complications are presented in Table 2. Four patients with thalamotomy were re-operated due to recurrence of tremor.

\textbf{Table 2}. Nature and number of hardware-related complications in Paper I and Paper II. In Paper I 129 procedures with implantation of 151 electrodes were performed, and in Paper II 139 procedures with 161 implanted electrodes.

<table>
<thead>
<tr>
<th>Lead fracture</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraoperative electrode migration</td>
<td>2</td>
</tr>
<tr>
<td>Late postoperative electrode migration</td>
<td>2</td>
</tr>
<tr>
<td>IPG migration</td>
<td>2</td>
</tr>
<tr>
<td>Erosion</td>
<td>3</td>
</tr>
<tr>
<td>Infection</td>
<td>2</td>
</tr>
<tr>
<td>Erosion + infection</td>
<td>2</td>
</tr>
<tr>
<td>Frequent external interference</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
</tr>
</tbody>
</table>

Patients with hardware related complications 17
Patients with more than one complication 4
Adverse events in patients with PD vs. ET:

Gait-disturbance after thalamic surgery was twice as high in patients with PD as in patients with ET.

Complications according to target:

Differences were seen in the profile of various complications between the different targets.

Complications according to target and procedure for the whole population are presented in Table 3. The adverse events in thalamic and pallidal surgery, according to unilateral versus bilateral procedures, and according to lesion versus DBS, are shown in Table 4 and 5, respectively.

Table 3. Number and percentage of adverse effects of lesioning and DBS according to target (Paper I).

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Thalamus (n = 96)</th>
<th>Thalamotomy (n = 51)</th>
<th>Pallidum (n = 11)</th>
<th>Pallidotomyc (n = 76)</th>
<th>STN DBS (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracerebral haemorrhage</td>
<td>1 (2.0%)</td>
<td>1 (2.0%)</td>
<td>1 (1.3%)</td>
<td>1 (4.5%)</td>
<td></td>
</tr>
<tr>
<td>Seizures</td>
<td>1 (1.0%)</td>
<td>1 (1.3%)</td>
<td>1 (1.3%)</td>
<td>2 (9.1%)</td>
<td></td>
</tr>
<tr>
<td>Quadrantanopsia</td>
<td>2 (2.6%)</td>
<td>2 (2.6%)</td>
<td>2 (2.6%)</td>
<td>1 (4.5%)</td>
<td></td>
</tr>
<tr>
<td>Confusion</td>
<td>6 (6.3%)</td>
<td>1 (2.0%)</td>
<td>1 (9.1%)</td>
<td>6 (7.9%)</td>
<td></td>
</tr>
<tr>
<td>Vasovagal reaction</td>
<td>1 (2.0%)</td>
<td>1 (9.1%)</td>
<td>1 (9.1%)</td>
<td>2 (9.1%)</td>
<td></td>
</tr>
<tr>
<td>Hypersalivation</td>
<td>2 (2.6%)</td>
<td>2 (2.6%)</td>
<td>2 (2.6%)</td>
<td>1 (4.5%)</td>
<td></td>
</tr>
<tr>
<td>Paresis /Dysequilibrium/</td>
<td>28 (54.9%)</td>
<td>3 (3.9%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gait-disturbance</td>
<td>6 (11.8%)</td>
<td>2 (18.2%)</td>
<td>2 (2.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysarthria</td>
<td>6 (11.8%)</td>
<td>2 (18.2%)</td>
<td>2 (2.6%)</td>
<td>4 (18.2%)</td>
<td></td>
</tr>
<tr>
<td>Hypophonia</td>
<td>1 (9.1%)</td>
<td>1 (1.3%)</td>
<td></td>
<td>2 (9.1%)</td>
<td></td>
</tr>
<tr>
<td>Blepharospasm</td>
<td>1 (9.1%)</td>
<td>1 (9.1%)</td>
<td></td>
<td>3 (13.6%)</td>
<td></td>
</tr>
<tr>
<td>Cognitive disturbance</td>
<td>1 (9.1%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disturbance</td>
<td>1 (9.1%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stimulation induced side effects</td>
<td>16 (16.7%)</td>
<td>16 (16.7%)</td>
<td></td>
<td>16 (16.7%)</td>
<td></td>
</tr>
<tr>
<td>(dysarthria, gait-disturbance)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rebound of symptoms</td>
<td>21 (21.9%)</td>
<td></td>
<td></td>
<td>2 (9.1%)</td>
<td></td>
</tr>
<tr>
<td>Hardware complications</td>
<td>16 (16.7%)</td>
<td>1 (1.3%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total no of adverse events</td>
<td>60 (62.5%)</td>
<td>38 (74.5%)</td>
<td>8 (72.7%)</td>
<td>18 (23.7%)</td>
<td></td>
</tr>
<tr>
<td>No of procedures with adverse events</td>
<td>45 (46.9%)</td>
<td>32 (62.7%)</td>
<td>5 (45.4%)</td>
<td>16 (21.1%)</td>
<td></td>
</tr>
<tr>
<td>No of procedures with more than one adverse event</td>
<td>14 (14.6%)</td>
<td>5 (9.8%)</td>
<td>2 (18.2%)</td>
<td>2 (2.6%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5 (22.7%)</td>
<td></td>
</tr>
</tbody>
</table>
Table 4. Thalamic surgery: Number and percentage of adverse effects of unilateral vim-DBS, unilateral thalamotomy and bilateral lesions / DBS respectively, in relation to number of procedures (Paper I).

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Unilateral Vim-DBS</th>
<th>Unilateral Unilateral</th>
<th>Unilateral Unilateral Vim-DBS &amp; contralateral thalamotomy</th>
<th>Bilateral Vim-DBS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 74</td>
<td>n = 51</td>
<td>n = 14</td>
<td>n = 7</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizure</td>
<td>1 (1.4%)</td>
<td>1 (2.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confusion</td>
<td>5 (6.8%)</td>
<td>1 (2.0%)</td>
<td>1 (7.1%)</td>
<td></td>
</tr>
<tr>
<td>Vasovagal reaction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypersalivation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pares / Dysequeilibrium/ Gait-disturbance</td>
<td>28 (54.9%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysarthria</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rebound</td>
<td>14 (18.9%)</td>
<td>4 (28.6%)</td>
<td>3 (42.9%)</td>
<td></td>
</tr>
<tr>
<td>Stimulation induced side-effects (dysarthria, gait-disturbance)</td>
<td>5 (6.8%)</td>
<td>5 (35.7%)</td>
<td>6 (85.7%)</td>
<td></td>
</tr>
<tr>
<td>Hardware complications</td>
<td>10 (13.5%)</td>
<td>2 (14.3%)</td>
<td>4 (57.1%)</td>
<td></td>
</tr>
<tr>
<td>Total nr of adverse events</td>
<td>35 (47.3%)</td>
<td>38 (74.5%)</td>
<td>12 (85.7%)</td>
<td>13 (185.7%)</td>
</tr>
<tr>
<td>No of procedures with adverse events</td>
<td>28 (37.8%)</td>
<td>32 (62.7%)</td>
<td>10 (71.4%)</td>
<td>7 (100%)</td>
</tr>
<tr>
<td>No of Procedures with more than one adverse event</td>
<td>7 (9.5%)</td>
<td>5 (9.8%)</td>
<td>2 (14.3%)</td>
<td>5 (71.4%)</td>
</tr>
</tbody>
</table>

Table 5. Pallidal surgery: Number and percentage of adverse effect of unilateral pallidal DBS, unilateral pallidotomy and bilateral lesions / DBS respectively, in relation number of procedures (Paper I).

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Unilateral PVP-DBS n = 4</th>
<th>Unilateral Pallidotomy n = 64</th>
<th>Bilateral Pallidotomy n =12</th>
<th>Unilateral PVP-DBS &amp; contralateral pallidotomy n = 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemorrhage</td>
<td>1 (1.6%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quadrantanopsia</td>
<td>2 (3.1%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confusion</td>
<td>6 (9.4%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasovagal reaction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypersalivation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transient paresis</td>
<td>2 (3.1%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysarthria</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypophonia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive disturbance</td>
<td>1 (25%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hardware complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total nr of adverse events</td>
<td>3 (75.0%)</td>
<td>14 (21.9%)</td>
<td>4 (33.3%)</td>
<td>5 (100.0%)</td>
</tr>
<tr>
<td>No of procedures with adverse events</td>
<td>3 (75%)</td>
<td>13 (20.3%)</td>
<td>3 (25.0%)</td>
<td>2 (40.0%)</td>
</tr>
<tr>
<td>No of Procedures with more than one adverse event</td>
<td>0</td>
<td>1 (1.6%)</td>
<td>1 (8.3%)</td>
<td>2 (40.0%)</td>
</tr>
</tbody>
</table>
The material included 119 patients undergoing 139 operations with implantation of 161 electrodes. Forty-nine procedures were performed for ET and 68 for PD. Three surgeons were involved in the procedures. The number of procedures according to brain target is presented in table 1.

The DBS electrode was anchored to the burr-hole using suture of lead with silicon tube in the first 48 cases, and using the Medtronic burr-hole cap (Medtronic, Minneapolis, MN, USA) in the subsequent cases. The connection between electrode and cable was placed in the upper neck area below the mastoid in the first 49 procedures and on the calvarium in the vicinity of the burr-hole in the subsequent procedures.

Two procedures were aborted during surgery, and 4 externalized electrodes were removed due to lack of effect of test-stimulation. The patients were followed post-operatively for a minimum of 12 months, except for one patient who died from cancer one month after surgery. The mean follow-up time in electrode-months, defined as the number of months with an electrode implanted, was 40 (range 1 - 117).

Complications

Twenty-three hardware related complications occurred in 17.3% of the procedures and 15% of the patients, yielding a complication rate per electrode-year of 4.3 %. Table 2 shows the number and nature of the complications. Figure 1 shows the complication-free time.

In two cases, postoperative imaging revealed per-operative dislocation of the electrode. In two other patients, the connection between electrode and extension cable on the neck migrated after the operation, dislocating the intracerebral electrode upwards. Surgical intervention was needed to reposition the electrodes.

Electrode breakage occurred in seven patients with ET and one with PD. The breakage occurred at the place where the electrode enters the connection cable. This did only
occur in patients with the connection placed on the neck, where the frequency of this complication was 16.7%. The mean time between implantation and breakage was 25 months (range 10 - 54).

One patient developed an infection secondary to a trauma over the IPG. Two cases of erosion and infection occurred over the connection between the cable and the intracerebral electrode. In a third case, an old patient in poor general condition presented 15 months after surgery with an erosion over the connection on the calvarium. This was revised and the patient was treated with antibiotics. The erosion recurred two months later and had to be re-revised. After 18 more months the erosion recurred again and the whole DBS system had to be extracted. In only one patient, a postoperative infection occurred early after surgery (within 2 months).

In two cases the Itrel II neurostimulator had to be replaced with a Kinetra, due to frequent episodes of external interference.

Figure 1. Kaplan-Meier plot showing complication-free time of 161 implanted electrodes (+ :time of complication) (Paper II).
Paper III

At surgery, 90 patients were implanted with an Itrel II neuropulse generator, 66 with Kinetra and 18 with Soletra. The patients were followed for a mean of 40 months (range 1-117 months).

Unintended deactivation of the implantable pulse generator (IPG): The IPG is equipped with a magnetic control circuit for activation/deactivation with an external magnet, and this function is susceptible to inadvertent deactivation by other electromagnetic forces in the environment besides the magnet. In our material 20 patients could identify a probable cause for the unintended shutdown of the system (12%). These cases are listed in Table 6 and further described in some detail below.

Table 6. Patients with unintended deactivation of the IPG (Paper III).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Target</th>
<th>IPG</th>
<th>Suspected source of interference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pat 1</td>
<td>STN</td>
<td>Itrel II</td>
<td>Theft-detector</td>
</tr>
<tr>
<td>Pat 2</td>
<td>Vim</td>
<td>Soletra</td>
<td>Theft detector, electric-weld</td>
</tr>
<tr>
<td>Pat 3</td>
<td>STN</td>
<td>Kinetra</td>
<td>Theft-detector</td>
</tr>
<tr>
<td>Pat 4</td>
<td>STN</td>
<td>Itrel II</td>
<td>Security-gate in airport</td>
</tr>
<tr>
<td>Pat 5</td>
<td>STN</td>
<td>Itrel II</td>
<td>Security-gate in airport</td>
</tr>
<tr>
<td>Pat 6</td>
<td>Vim</td>
<td>Itrel II</td>
<td>Security-gate in airport</td>
</tr>
<tr>
<td>Pat 7</td>
<td>STN</td>
<td>Itrel II</td>
<td>Security-gate in airport, loud-speaker</td>
</tr>
<tr>
<td>Pat 8</td>
<td>STN</td>
<td>Itrel II</td>
<td>Loud-speaker</td>
</tr>
<tr>
<td>Pat 9</td>
<td>STN</td>
<td>Itrel II</td>
<td>Loud-speaker</td>
</tr>
<tr>
<td>Pat 10</td>
<td>Vim</td>
<td>Itrel II</td>
<td>Loud-speaker</td>
</tr>
<tr>
<td>Pat 11</td>
<td>STN</td>
<td>Itrel II</td>
<td>Voice-memory</td>
</tr>
<tr>
<td>Pat 12</td>
<td>STN</td>
<td>Itrel II</td>
<td>Mobile phone</td>
</tr>
<tr>
<td>Pat 13</td>
<td>STN</td>
<td>Itrel II</td>
<td>Dentist-visit</td>
</tr>
<tr>
<td>Pat 14</td>
<td>Vim</td>
<td>Itrel II</td>
<td>Dentist-visit</td>
</tr>
<tr>
<td>Pat 15</td>
<td>Vim</td>
<td>Itrel II</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>Pat 16</td>
<td>STN</td>
<td>Itrel II</td>
<td>Lightening-rod</td>
</tr>
<tr>
<td>Pat 17</td>
<td>Gpi</td>
<td>Itrel II</td>
<td>Electric-weld, electric drill-bur</td>
</tr>
<tr>
<td>Pat 18</td>
<td>STN</td>
<td>Itrel II</td>
<td>Security-cortege</td>
</tr>
<tr>
<td>Pat 19</td>
<td>STN</td>
<td>Kinetra</td>
<td>Electric network / high voltage line</td>
</tr>
<tr>
<td>Pat 20</td>
<td>Gpi</td>
<td>Kinetra</td>
<td>Electric network / high voltage line</td>
</tr>
</tbody>
</table>
Two patients reported repeated problems when they were switching off or turning on the IPG with the external magnet. It was found that they, while testing stimulator functions with a transistor radio, held the loudspeaker against the IPG. Patients not equipped with a patient programmer often use a transistor radio to decide whether the stimulation is on or off. When moving the radio over the IPG, a disturbance will be heard on the AM-band, when the IPG is on. The loud-speaker should however not be placed directly over the IPG.

One patient was repeatedly admitted to the hospital due to unintended deactivation of the left IPG by his mobile phone. The patient used to place this in close proximity to his implanted IPG, when speaking. For cardiac pacemakers, it has been generally thought that a typical consumer mobile phone has to be within 10 cm to cause interference with a pulse generator, and that this is unlikely to occur during typical mobile telephone use 123.

One patient with an Itrel II fainted while using an electrical welding machine. After this episode the IPG started to turn itself on and off randomly. The stimulator was removed for examination, and showed irreversible damage to the magnet on/off switching mechanism. The IPG was replaced with another Itrel II, but the problems did not disappear completely, until the Itrel II was replaced by a magnetically shielded Kinetra. In another patient the Itrel II also had to be replaced with a Kinetra due to repeated DBS deactivations.

Two patients experienced worsening of symptoms after working with an electric network, close to high-voltage lines. Their Kinetras, with enabled magnet control, had been unintentionally deactivated.

One patient with bilateral stimulation repeatedly experienced random switching off and on of his Itrel II IPG, while the security-cortège of the Lebanese premier minister was passing by his house. A similar phenomenon was reported by a patient with a cardiac pacemaker living along the same street. The possible explanation for this is that the convoy
employed a high-energy radio-jamming device. This equipment creates an intensive electromagnetic field with a specialized spectrum that serves as interference for other local radio signals by saturating a wide frequency range. This includes frequencies commonly used for eavesdropping and activation of remote explosive devices.

**Magnetic Resonance Imaging:** MRI of the brain was performed in 74 of our patients with implanted electrodes. The majority of these were performed before implantation of the IPG. In chronically stimulated patients, the stimulation was switched off and the voltage was set to zero prior to MRI. None of these patients had any negative effects.

Two patients underwent MRI with their Kinetras still on stimulation, and with the magnetic control disabled. In one of the patients a MRI of the leg was performed and in the other a MRI of the left shoulder (right above the implanted Kinetra). No interference was noted. In another patient the Itrel II IPG had been turned off, but not set to zero before the MRI, and the patient experienced repeated episodes of paresthesias. When resuming the investigation, after setting the amplitude to zero, no paresthesias were reported. These MRI induced paresthesias were probably caused by repeated activation and deactivation of the stimulator.

**Interference from hearing loop:** One patient with DBS and a hearing device based on a hearing loop got headache each time she sat on the cushion connected to the hearing loop. One possible mechanistic explanation for this is that the fields generated by the T-coil system could affect the DBS lead, which is acting like an antenna.

**Electrocautery:** One patient underwent surgery with monopolar electrocautery without negative effects.

**Electrocardiogram (ECG):** In one patient the IPG was deactivated during ECG recordings. In some patients with DBS, artefacts occurred on the ECG, making this difficult to interpret.
*Heart defibrillation:* Several patients underwent heart defibrillation, both acutely with the stimulation on, and planned with the IPG voltage set to zero and turned off. In neither case was the subsequent function of the DBS hardware affected, nor did the patients sustain any apparent neurological injury.

*Cardiac pacemakers:* Three patients with DBS were implanted with cardiac pacemakers because of bradycardia with AV-block III. In the first patient, DBS settings were monopolar. This patient suffered several episodes of syncope. After switching DBS to bipolar mode, syncope did not recur. The other patients were set to bipolar stimulation in order to avoid interference with the cardiac pacemaker.

Three patients received intracardial defibrillators (ICD). In one of these patients bilateral monopolar DBS apparently induced recurrent ventricular arrhythmias and cardiac defibrillations, up to 200 times per day, which necessitated admission to the cardiac care unit for monitoring and treatment. The arrhythmia was refractory to anti-arrhythmic drugs despite multiple drug and dosage adjustments. Bilateral adjustment of the DBS to a bipolar mode finally prevented recurrence of this patient’s arrhythmias. Two other patients with ICDs received DBS, and bipolar stimulation did not result in any apparent negative effects.
**Paper IV**

The patient was right-handed 62 year old man, with Parkinson’s disease, referred for bilateral STN-DBS. The patient had no cognitive or psychiatric disorders, except for a mild depression that was well controlled on medication. During surgery stimulation of the most distal contact on the right side resulted in an unexpected side-effect. Within a couple of seconds the patients face showed an expression of outmost sorrow and he started to sob and cry violently. The patient said repeatedly that “everything is so dark”, “please doctor I don’t want to live”. Upon direct questioning, the patient said that he was very depressed. The stimulation was stopped and within 10 seconds the patient stopped crying and returned to his previous mental status. When questioned, the patient confirmed that he had felt terribly depressed during the stimulation, combined with a feeling of going into a darkness, but that the feelings of depression now had resolved. The stimulation was repeated several times with the same result. When stimulating at the higher contacts, no emotional response was elicited. The electrode was subsequently retracted two mm and anchored in this position. The procedure was then repeated on the left side, where no emotional effects were observed.

An immediate postoperative thin-slice MRI was performed showing a good localisation of the electrodes in the STN, with the lowest contact of the right electrode in the substantia nigra (SN) (Fig 2). This means that the most ventral contact zero of the right electrode before retraction was located in the ventral substantia nigra. During the subsequent programming of the stimulation no affection of mood was noticed.

The patient has now been followed for five years. During this period no affection of the mood has been noted.
Figure 2 a & b (paper IV).

a. A coronal scan, two-mm-thick, showing the right-sided electrode with its tip in the dorsal substantia nigra. The MRI was performed after that the right-sided electrode had been pulled out 2 mm during surgery. The right electrode is localized more medially than the left one, in the medial part of the substantia nigra, which consists mainly at this level of the pars compacta with only few dispersed neurons of the pars reticulata.

b. Two adjacent, 2-mm-thick, axial scans. The left scan shows the tip of the right-sided electrode in the substantia nigra. The right scan is more dorsal and shows that the electrode contact is in the STN.
The initial pallidotomy was performed contralateral to the most affected side of the body. Three left-sided and two right-sided pallidotomies were performed, and, subsequently, two left-sided and three right-sided pallidal DBS. The mean age of the patients at first surgery was 64 years (range 53 -79). The mean time between the pallidotomy and the contralateral DBS was 14 months (range 10 -21). The latest evaluation was done 37 months (range 22-60) after the pallidotomy and 22 months (range12-33) after the pallidal DBS.

The locations of the lesions and the DBS electrodes were verified on postoperative thin-slice MRI and / or CT scans (Fig. 3).

Figure 3. Remote post-operative coronal MRI scan showing the left sided pallidotomy and the DBS lead in the right pallidum (Paper V).
Efficacy of surgery

The mean preoperative UPDRS part III (motor) score for the patients (worst off state) was 49 (range 46-53), and postoperatively at the last evaluation 33 (range 16-44) (32.7% improvement, p<0.05). The UPDRS part II (Activities of Daily Living) scores changed from 24.8 (range 16 – 36) preoperatively to 21.2 (range 15 – 25) at last evaluation, (p = n.s.). Table 7 shows patient characteristics, H&Y, S&E and UPDRS II and III preoperatively and at last follow up.

The scores of appendicular items no. 20-26 of UPDRS part III of the side contralateral to pallidotomy are shown in table 8. The scores of items 32-35 of UPDRS part IV are shown in Table 9.

Complications

No peri- or postoperative complications occurred in connection with the initial pallidotomies. Concerning the pallidal DBS procedures, one patient had a reversible postoperative confusion. Two patients exhibited dysarthria and one patient showed a severe worsening of dysphonia following DBS. The dysarthria was partly reversible if stimulation was altered or stopped but the dysphonia was irreversible regardless of stimulation changes. One case of frequent external affection of the DBS system necessitated replacement of the Itrel II with a Kinetra.
Table 7. Patient characteristics, Hoehn and Yahr (H&Y), Schwab and England scale (S&E) and the Unified Parkinson’s Disease Rating Scale (UPDRS) part II and III, preoperatively and at last follow up, in worst-off condition (Paper V).

<table>
<thead>
<tr>
<th></th>
<th>Preoperative</th>
<th>Last follow up</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>64 (53-79)</td>
<td>67 (57-81)</td>
<td></td>
</tr>
<tr>
<td>H&amp;Y</td>
<td>4.2 (4-5)</td>
<td>3.9 (3-5)</td>
<td>n.s.</td>
</tr>
<tr>
<td>S&amp;E</td>
<td>44 (20-60)</td>
<td>60 (50-70)</td>
<td>n.s.</td>
</tr>
<tr>
<td>UPDRS II</td>
<td>24.8 (16-36)</td>
<td>21.2 (15-25)</td>
<td>n.s.</td>
</tr>
<tr>
<td>UPDRS III</td>
<td>49 (46-53)</td>
<td>33 (16-44)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>L-dopa- equivalents</td>
<td>945 mg (400-1300)</td>
<td>1095 mg (500-2250)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Table 8. Appendicular items no. 20-26 of the Unified Parkinson’s Disease Rating Scale part III (tremor, rigidity, finger taps, hand grips, hand pronate/supinate, leg agility) of the side contralateral to surgery, pre- and postoperative at last follow up, in worst-off condition (Paper V).

<table>
<thead>
<tr>
<th></th>
<th>Preop score</th>
<th>Postop score</th>
<th>% change</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>contralateral to pallidotomy:</td>
<td>14.4 ± 2.9 (range 12-18)</td>
<td>9.7 ± 4.8 (range 4-16)</td>
<td>32.5%</td>
<td>0.048</td>
</tr>
<tr>
<td>contralateral to pallidal DBS:</td>
<td>13.2 ± 5.9 (range 6-21)</td>
<td>9.9 ± 3.7 (range 6-15)</td>
<td>25%</td>
<td>n.s.</td>
</tr>
<tr>
<td>P value:</td>
<td>n.s.</td>
<td>n.s.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 9. Appendicular items no. 32-35 of the Unified Parkinson’s Disease Rating Scale part IV (dyskinesias and dystonia) of the side contralateral to surgery, pre- and postoperative at last follow up, in medication-on condition (Paper V).

<table>
<thead>
<tr>
<th></th>
<th>Preop score</th>
<th>Postop score</th>
<th>% change</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>contralateral to pallidotomy:</td>
<td>6.6 ± 1.9 (range 4-9)</td>
<td>0.6 ± 0.9 (range 0-2)</td>
<td>91%</td>
<td>0.001</td>
</tr>
<tr>
<td>contralateral to pallidal DBS:</td>
<td>4.4 ± 1.5 (range 3-7)</td>
<td>1.8 ± 1.5 (range 0-4)</td>
<td>59%</td>
<td>0.003</td>
</tr>
<tr>
<td>P value:</td>
<td>n.s.</td>
<td>n.s.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Paper VI

The 19 patients have been followed for a mean time of 104 ± 10 (SD) months (range 84-118). The mean age at the time of surgery was 68, and at final evaluation 75 years.

Tremor assessment

The ETRS scores and their evolution over time are presented in table 10. The total ETRS score demonstrated a statistically significant deterioration from the preoperative mean value of 58 to 68 ‘off’ stimulation at the last evaluation. This increase was mainly due to an increase in activities of daily living (ADL) and tremor-scores of the ipsilateral hand. The improvement in the total ETRS score from the ‘off’ stimulation state to the ‘on’ stimulation state was significant at both evaluations with 29 at the initial, and 47 at the last follow up.

Part A of the ETRS (item 1-9) showed a significant improvement when ‘on’ stimulation was compared with off stimulation and with baseline. The greatest improvement was observed concerning item 5/6, tremor of the contralateral upper extremity, with a reduction from the initial score of 6.8 to 1.2 (82.4%) at the initial follow up and 2.7 (60.3%) at the last evaluation.

Items 11-14 of part B of the ETRS, rating the function of the hand, demonstrated a contralateral reduction on stimulation from 12.7 to 4.1 (67.7%) and 8.2 (35.4%), respectively, at initial and last follow-up. This reduction was statistically significant both when compared to baseline and to off stimulation.

ADL (item 15-21) deteriorated significantly from 14.3 at baseline, to 20.1 during ‘off’ stimulation at last evaluation. The improvement from baseline with stimulation, to 5.4 and 13.6, at each evaluation respectively, was significant only for the initial evaluation.
There was, however, a significant improvement between ‘on’ and ‘off’ stimulation at both evaluations.

*Stimulation parameters*

The mean number of patient visits for alteration of parameter settings was 0.8 per year. Initially all patients had monopolar stimulation, but the number of patients with bipolar stimulation increased to 32% after 7 years. Pulse effective voltage (PEV) has been used as a measurement of stimulation strength and is calculated\(^235\) as \(\sqrt{U^2 \times pps \times pw}\), where U = voltage (V), pps = pulses per second (Hz) and pw = pulse-width (µs). At one month after surgery, the mean stimulation parameters were 1.5 V, 65 µs and 153 Hz, yielding a PEV of 0.15 V. A gradual increase was observed during follow-up, and after 7 years the mean values were 2.6 V, 68 µs, 171 Hz and 0.29 V, respectively. The increase in voltage, PEV and frequency was statistically significant \((p \leq 0.0001 \text{ ANOVA}, p \leq 0.01 \text{ post hoc test})\). The stimulation parameters and their evolution over time are presented in table 11.

*Complications and battery depletion*

Six patients underwent re-operation due to lead-breakage. One of these patients also underwent revision of the IPG-pocket. The Itrel II IPG was replaced due to battery-depletion in 12 patients after a mean time of 84 ± 18 months. Thus, the original IPG was still functioning in 7 patients after a mean time of 99 ± 9 months. The cumulative survival of the IPG is presented in Figure 4.
Table 10. ETRS scores in 19 patients at baseline before surgery, and on and off stimulation at initial evaluation after 13 ± 4.9 months and final evaluation after 86 ± 9.0 months (Paper VI).

<table>
<thead>
<tr>
<th>Item</th>
<th>Maximum Score</th>
<th>Baseline Stimulation</th>
<th>Initial evaluation Stimulation</th>
<th>Final evaluation Stimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Off</td>
<td>On</td>
<td>Off</td>
</tr>
<tr>
<td>Sum ETRS (item 1-21)</td>
<td>144</td>
<td>57.6 ± 19.2</td>
<td>60.7 ± 18.7</td>
<td>29.2 ± 14.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>68.1 ± 22.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>47.4 ± 21.0</td>
</tr>
<tr>
<td>Part A (item 1-9)</td>
<td>80</td>
<td>17.1 ± 8.5</td>
<td>15.4 ± 7.6</td>
<td>8.0 ± 4.8**</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>19.3 ± 9.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11.7 ± 6.9**</td>
</tr>
<tr>
<td>Voice tremor (item 3)</td>
<td>4</td>
<td>0.7 ± 1.0</td>
<td>0.6 ± 1.0</td>
<td>0.4 ± 0.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.8 ± 1.2</td>
</tr>
<tr>
<td>Head tremor (item 4)</td>
<td>8</td>
<td>1.5 ± 1.9</td>
<td>0.9 ± 1.3</td>
<td>0.5 ± 0.8**</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.1 ± 1.7</td>
</tr>
<tr>
<td>Tremor of upper extremity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ipsilateral to DBS</td>
<td>12</td>
<td>5.1 ± 3.1</td>
<td>5.0 ± 2.5</td>
<td>5.0 ± 2.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6.7 ± 3.5</td>
</tr>
<tr>
<td>contralateral to DBS</td>
<td>12</td>
<td>6.8 ± 3.1</td>
<td>7.4 ± 3.0</td>
<td>1.2 ± 1.7**</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7.1 ± 2.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.7 ± 2.5**</td>
</tr>
<tr>
<td>Rest</td>
<td>4</td>
<td>0.8 ± 1.4</td>
<td>1.0 ± 1.6</td>
<td>0.0 ± 0.0*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.1 ± 1.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.3 ± 0.9†</td>
</tr>
<tr>
<td>Postural</td>
<td>4</td>
<td>2.5 ± 1.4</td>
<td>2.7 ± 1.4</td>
<td>0.2 ± 0.4*††</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.7 ± 1.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.5 ± 1.0**</td>
</tr>
<tr>
<td>Activity/intention</td>
<td>4</td>
<td>3.5 ± 1.0</td>
<td>3.6 ± 0.8</td>
<td>1.1 ± 1.5**††</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.4 ± 1.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.0 ± 1.8**</td>
</tr>
<tr>
<td>Hand function (item 11-14)</td>
<td>32</td>
<td>26.2 ± 8.0</td>
<td>28.1 ± 8.6</td>
<td>15.8 ± 7.7**</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25.6 ± 9.2</td>
</tr>
<tr>
<td>Contralateral to DBS</td>
<td>16</td>
<td>12.7 ± 3.1</td>
<td>13.3 ± 4.3</td>
<td>4.1 ± 3.0**</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12.5 ± 5.3</td>
</tr>
<tr>
<td>Ipsilateral to DBS</td>
<td>16</td>
<td>11.2 ± 5.2</td>
<td>11.9 ± 4.7</td>
<td>11.5 ± 4.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>13.1 ± 4.5</td>
</tr>
<tr>
<td>ADL (item 15-21)</td>
<td>28</td>
<td>14.3 ± 6.2</td>
<td>17.2 ± 6.0**</td>
<td>5.4 ± 4.3**††</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20.1 ± 6.7**</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>13.6 ± 7.7††</td>
</tr>
</tbody>
</table>

Values are mean (SD).

*Significant vs. baseline P ≤ 0.05. **Significant vs. baseline P ≤ 0.01.
†Significant on vs. off stimulation P ≤ 0.05. ††Significant on vs. off stimulation P ≤ 0.01.

.Item 10 – 21 could not be completed at final evaluation in one case due to dementia.

Essential tremor rating scale (ETRS), deep brain stimulation (DBS), activities of daily living (ADL).

Table 11. Stimulation parameters and pulse effective voltage presented with mean values (SD) (Paper VI).

<table>
<thead>
<tr>
<th></th>
<th>1 month</th>
<th>1 year</th>
<th>3 years</th>
<th>5 years</th>
<th>7 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mono-/bipolar</td>
<td>19/0</td>
<td>18/1</td>
<td>17/2</td>
<td>16/3</td>
<td>13/6</td>
</tr>
<tr>
<td>Voltage (V)</td>
<td>1.5 ± 0.3</td>
<td>1.8 ± 0.7</td>
<td>2.3 ± 0.8</td>
<td>2.4 ± 0.8</td>
<td>2.6 ± 0.9</td>
</tr>
<tr>
<td>Pulse-width (µs)</td>
<td>65 ± 11</td>
<td>68 ± 14</td>
<td>68 ± 14</td>
<td>63 ± 9</td>
<td>68 ± 14</td>
</tr>
<tr>
<td>Frequency (Hz)</td>
<td>153 ± 10</td>
<td>164 ± 15</td>
<td>168 ± 16</td>
<td>167 ± 17</td>
<td>171 ± 7</td>
</tr>
<tr>
<td>Pulse effective voltage (V)</td>
<td>0.15 ± 0.03</td>
<td>0.20 ± 0.09</td>
<td>0.24 ± 0.10</td>
<td>0.24 ± 0.09</td>
<td>0.29 ± 0.11</td>
</tr>
</tbody>
</table>

Figure 4. Kaplan-Meier plot demonstrating the cumulative survival of the implanted pulse-generator in 19 patients. Depletion-time of the battery is marked (Paper VI).
DISCUSSION

Paper I-IV

Even though several conclusions can be drawn from paper I concerning complications of lesioning and DBS, it is not possible to make a head to head comparison between these methods. Differences between the two procedures/groups include the following: selection of brain target, no subthalamotomies in this material, large differences in numbers between some of the sub-groups, uni- and bilaterality of surgery, developments in surgical and imagine-techniques during the study-period, and possibly other things. To gain more definitive knowledge about side effects of lesions vs. DBS, a prospective randomized study would be necessary. The report does, however, provide a description of the clinical reality during this period. The findings of paper I concerning hardware-related complications and external electromagnetic influences was only briefly discussed in the original paper. These areas will here be discussed based on paper II and III, respectively.

In paper I, the groups with lesions and DBS were identical concerning age and sex distribution, but there were differences according to diagnosis as well as according to target. More importantly, several of the complications were more or less specific for a certain target and / or surgical procedure.

Some of the reported complications are target-independent, i.e. haemorrhages, seizures and vasovagal reactions etc. These complications were rare and did not differ between lesional vs. DBS procedures.

*Haemorrhages:* Haemorrhages occurred with a frequency of 1.6% in the lesion group and 0.8 % in the DBS group. These bleedings occurred as a result of passing the electrode and not as a result of lesioning. One procedure was aborted without lesioning, and
in the other case the subcortical bleeding, that occurred four days after surgery, was located far away from the lesion. It has been suggested that the process of lesioning carries a higher risk for haemorrhages, as a consequence of lesioning itself. This was not supported by our observations, nor by the findings of Favre et al. A higher incidence of ICH has been suggested when using multiple track microelectrode recording, and perhaps our relatively low incidence of ICH might reflect the low number of passes during surgery. None of the three patients had any neurological sequelae due to the haemorrhage.

Confusions: The causes of the intra- and postoperative confusions are not clear. The fact that almost all confusions occurred in patients with PD, might be due to a higher vulnerability of the brain, as compared to patients with ET.

Some complications are more or less specific for a certain target, i.e. quadrantanopsia secondary to pallidotomy. It is therefore necessary to compare the different methods, i.e. lesion vs. DBS according to each target: thalamotomy vs. thalamic DBS, and pallidotomy vs. pallidal DBS.

Thalamotomy vs. thalamic DBS:
A total of 38 initial complications occurred in 32 of the 51 patients operated with unilateral thalamotomy. Of these, 34 were so called “cerebellar”, with dysarthria, ataxia and disturbance of gait. At follow-up after four months, only 23.5% of these “cerebellar” complications were totally in regress. Even tough the majority of these complications were mild, their incidence was high.

In the group with unilateral thalamic DBS the frequency of adverse effects was 47.3%, affecting 37.8% of the patients. None of these were permanent in the absence of stimulation. The 25.7% adverse effects which constituted rebound and “accepted” stimulation-induced side effects are to be considered as permanent, since the only way to
avoid these would have been to abandon the therapy. Stimulation-induced side effects, such as dysarthria, dysequilibrium and disturbance of gait could generally be adapted with changing of stimulation parameters. In 6.8 % of the cases it was however necessary to accept these side-effects, in order to maintain an acceptable effect on the tremor. These reversible accepted stimulation induced side effects compare very favourably to their equivalents among the thalamotomies, where lesioning resulted in irreversible albeit slight weakness, gait disturbance or dysarthria in a much higher proportion.

Those patients who had bilateral surgery, either DBS following a contralateral thalamotomy, or bilateral DBS, had 52.4% of stimulation-induced side effects. The number of patients is too small, however, to draw definite conclusions concerning any differences between the group with bilateral Vim-DBS and the one with DBS combined with thalamotomy. Rebound was a relatively common phenomenon, and constituted a severe problem in several patients, as we have reported earlier119.

Several reports have showed that the efficiency of Vim-DBS is equal or superior to thalamotomy and that the number of complications have been higher in thalamotomies than in DBS223,257,288. Our results are in concordance with these reports, and we have therefore abandoned this method in favour of Vim-DBS in patients with tremor.

**Pallidotomy vs. pallidal DBS:**

A total of 18 adverse events occurred in 16 out of 76 pallidotomies. Transient complications of unilateral procedures occurred in 17.2% of patients, and permanent in 4.7%. In other studies, figures of 7.9% - 69.2% transient complications and zero to 19.2% permanent complications have been reported56,60-63,170. In our patients with staged bilateral pallidotomies 25% had transient side effects, and 8% permanent. The group of patients with bilateral pallidotomies was too small, however, to allow any conclusions to be drawn.
Eight adverse effects occurred in 5 of the 11 patients with pallidal DBS. Side effects were thus proportionately more common in this group than in the pallidotomy group. The majority of pallidal DBS procedures were, however, part of bilateral procedures, either bilateral DBS or unilateral pallidotomy with a subsequent contralateral pallidal DBS. It is well known that bilateral procedures carry a higher frequency of complications than unilateral procedures. The Parkinson disease study group reported 20 adverse events in a group of 38 bilaterally operated patients. Lyons et al. reported at long-time follow-up 13 adverse events in a group of nine patients undergoing pallidal DBS, five of which were bilateral. Loher et al. presented 16 patients, of which six were unilateral. The rate of complications in his group was 12.5%.

It has not been reported that unilateral pallidal DBS is superior to pallidotomy, neither concerning efficacy, nor concerning risks. Our own material has not shown pallidotomy to be a more dangerous procedure. Whenever unilateral pallidal surgery is indicated, we still consider unilateral pallidotomy to be a viable alternative to unilateral DBS. For bilateral procedures, either bilateral DBS or a combination of pallidotomy and contralateral DBS, may be considered.

**STN-DBS:**

Of the 23 adverse effects encountered in 10 (of 22 total) patients operated on with STN-DBS, 68.1% were transient and 36.4% permanent. Most notable of these adverse effects were the psychiatric side effects, which were only encountered after STN-stimulation, and these occurred in our initial and probably less stringently selected patients. Depression after STN-stimulation has been reported frequently. The depressions have most often been attributed to the reduction of L-dopa. In order to decrease the risk of these complications, every patient who is considered for STN-DBS at our institution is nowadays
thoroughly evaluated preoperatively concerning cognitive and psychiatric status. Further, in our current protocol, the doses of dopaminergic drugs are carefully and slowly reduced postoperatively.

One must however keep in mind that stimulation in the STN and its immediate vicinity has been reported to give rise to a variety of cognitive and psychiatric complications that are unlikely to be due to reduction of L-dopa\textsuperscript{9,24,66,83,118,133,160,165,166,188,229,246,248,252,290,291,301,305}. This was also demonstrated in paper IV where transient stimulation of a restricted area in the ventral substantia nigra, which is one of the main output systems of the basal ganglia, gave rise to reversible depressive symptoms independent of the clinical benefit derived from stimulation of other contacts within the STN proper. Bejjani et al\textsuperscript{15} described a similar case, where an electrode in the left SNR during stimulation gave rise to acute severe depressive symptoms. In their patient, as in our case, the patient became deeply depressed, cried and expressed the wish not to live any longer. The effect and the ending of the effect were, as in our case, almost immediate to the stimulation. A further similarity is that the patient described by Bejjani et al reported a feeling of being sucked into a black hole, while our patient reported that he was disappearing into darkness. In contrast to Bejjani et al who evaluated their patient some weeks after surgery, we did not notice any hypomania after the intra-operative stimulation was switched off. Kumar et al\textsuperscript{168} have mentioned one patient with unilateral STN-stimulation, where acute stimulation-induced depression was confined to a single contact. Doshi et al\textsuperscript{66} presented two cases with chronic bilateral STN-stimulation in whom changing of the active contacts led to acute depression, that instantaneously was relieved when the stimulation was reversed to the previous settings.

Kulisevsky et al\textsuperscript{165} reported three patients with bilateral STN-stimulation who during the first postoperative week developed mania. The active contacts were reported to have probably surpassed the substantia nigra. When at the end of the first postoperative week
higher located contacts were used, the mania gradually disappeared. Romito et al presented two cases of mania and hypersexuality, developing within days after bilateral STN-stimulation. Krack et al present two cases of STN-stimulation where stimulation induced feeling of well-being, merriment and mirthful laughter.

Depression secondary to STN-DBS is partly likely to be a consequence of reduction of L-DOPA. It appears gradually some time after surgery when the patient is on chronic stimulation. In our case as well as Bejjani et al’s, it was acute stimulation in the SN that gave rise to an acute depression. At this level, the SN is characteristically formed by mainly pars compacta neurons with only few scattered neurons of pars reticulata. It may well be that stimulation in the STN and the surrounding area can have psycho-modulating effects. Mallet et al reported two patients with Parkinson’s disease and obsessive-compulsive disorder, where stimulation in the STN area, including in the medial part of the Zona incerta, had an excellent effect on the obsessive-compulsive symptoms. These observations strengthen the need for more research into the neuro-psychiatric role of the subthalamic nucleus and its surroundings, and may open new possibilities for treatment of psychiatric and affective disorders.

**Hardware-related complications:**

Adverse events specific to DBS, irrespective of target and disease, are stimulation induced side effects, hardware related complications and interference with stimulation from external electromagnetic sources.

Hardware-related complications occurred in 13.2% of the patients with DBS in paper I, or at a rate of 4.7% per electrode-year. The corresponding observations for paper II were 15 % and 4.3 %, respectively. The incidence of hardware related complications in other studies has been between 4.3 – 49 %. These findings are most often
representative of a limited follow up time, while the implants are for life. Since DBS is a life-
long therapy, the only reasonable way to present the complication-rate is in electrode-years. Our incidence of hardware-related complication may compare favourably with similar studies which have presented figures between 7.7 % – 9.5 %. However, our follow-up time was considerably longer than in some other studies, and the incidence of complications seems to decrease with time (Fig. 1). It is notable from our material that the complications occurred after a mean period of 15.7 months after surgery.

It is obvious that a learning curve exists and that several of these hardware-related complications might be avoidable. The majority of these complications occurred in patients operated on during the first four years of our experience with DBS. After changing the location of the connector from the neck to the calvarium, and using a better device to anchor the electrode to the skull, we have no longer encountered any case with the hitherto most frequent hardware-related complications, i.e. lead fracture and electrode migration.

Surgically avoidable complications

Electrode breakage: Fracture of the electrode occurred only when the connector between extension cable and electrode was located below the mastoid, never when located at the calvarium. The increased risk for electrode-breakage at this localisation has been pointed out earlier by Schwalb et al, who reported 42% of cable-breakage. It seems possible that the movements in the neck, increasing the stress at the connector site, cause this. An interesting fact is that 7 out of our 8 electrode breakages occurred in patients with ET, probably due to head tremor in some cases, combined with a higher mobility of these patients, compared to that of parkinsonian patients.

Electrode migration: Downward migration of the connector was responsible for upwards dislocation of the DBS lead in two patients. In these patients, the fixation of
electrode to the burr-hole was performed using suture and a silicon tube around the electrode. In the literature, migration of the connector from the parietal to the cervical area has been pointed out as a cause of lead fracture. Hamel et al have suggested that this might be avoided by suturing the connector to a mini-plate or to the periosteum\textsuperscript{110}. However, since we started to use the Medtronic burr-hole cap to fixate the electrode, there were no more dislocations of the electrode.

\textit{Erosion and infection:} The placement of the connector at the calvarium might theoretically increase the risk of skin erosion. As has been reported earlier, most cases of erosion occur over the connector. We identified four cases with skin erosion overlying the connector. Three of these occurred at the skull, and one at the neck. After we started to use the new Medtronic low profile connection cable, skin erosion has not happened. No erosions occurred over the burr-hole, neither when the electrode was sutured to the bone, nor when the Medtronic burr-hole cap was used. Perhaps the fact that we use a small skin flap and not a linear incision over the burr-hole area, may have contributed to avoid the risk of this particular complication.

Factors that may influence the frequency of infections are the length of surgery, prophylactic administration of antibiotics, handling of the implants, and placement of the implants in relation to skin-incisions. To avoid infections, we have administered antibiotics prophylactically for three days. The length of the surgery in our cases was fairly short, in mean 4 h including implantation of stimulator. Care was taken not to place bulky parts of the implant directly under skin-incisions. The frequency of infection was 3\%. In other studies infections have occurred with an incidence between zero and 12.2\% \textsuperscript{23,146,157,213}. 
**External electromagnetic influences**

External electromagnetic influences constitute a special form of hardware-related side effect, where electromagnetic forces in the environment, often in the form of medical equipment, affect the function of the IPG. Several sources of electromagnetic interference have been identified, with different degrees of clinical consequences and safety relevance:

*Unintended deactivation:* Identifying unintended deactivation of the IPG was easy for patients with tremor-dominant disease; the resulting lack of effect when devices were inadvertently turned off was often noticed directly by the patients, who then switched the IPG on by themselves. In this group of patients, who mainly had Vim-DBS for tremor, unintended deactivation was most often reported spontaneously by the patient. To identify and to determine the exact moment of unintended deactivation is more difficult for patients with non tremor-dominant disease, who are usually treated with pallidal or STN-DBS. Non-intended deactivation was also identified when the memory of the IPG was checked. This was possible, however, only in patients who typically had 24-hour/day stimulation, that is, patients with DBS in the STN and pallidum. Some of the patients with Vim-DBS had a remarkably high frequency of switching on and off, but this was interpreted as a sign of patient uncertainty in their own management of the magnet-driven functions.

External electromagnetic interference that leads to inadvertent deactivation of the IPG is a widely recognised phenomenon. Typically, this event is very occasional if it occurs, and is managed by the patient him/herself by merely turning the stimulator on again. However, some patients deteriorate in their motor function severely following inadvertent and unrecognised deactivation of the IPG. In some patients, unintended deactivation of the IPG might constitute a medical emergency, and this fact has led us to offer to the majority of our patients the magnetically shieldable Kinetra IPG, even for unilateral procedures.
Furthermore, in most cases where unintended switching off of the IPG is recurrent, we replace the Itrel II IPG with the magnetically shielded Kinetra.

The default magnet control of Kinetra can be inactivated, and there has been no reported case to our knowledge of unintended deactivation of Kinetra when the magnet control function had been disabled. The patients are provided with a patient programmer which allows them to check their IPG, and if necessary to reactivate function. Patients are further educated concerning how to identify and manage unintended machine deactivation.

**MRI:** The phenomenon of repeated activation and deactivation of the IPG in proximity to MRI has been reported, sometimes up to several hundred times during one examination. Because of this repeated activation and deactivation during MRI, it is now recommended that the voltage be set to zero before MRI is performed.

It has been demonstrated by several authors, with *in vitro* as well as *in vivo* studies, that MRI does not cause any damage when performed on patients with implanted DBS electrodes under normal clinical settings and using a transmitter-received headcoil. These tests have been performed with externalized as well as internalized neurostimulators. However, *in vitro* studies have shown that MRI can cause excessive heating of the electrode-tip during certain MRI operational conditions. Two cases describing presumed excessive heating of the electrode have been reported. Spiegel et al. described one case where MRI with a 1-Tesla unit and head coil was performed in a patient with bilaterally externalised STN-electrodes. The externalised cables were fixed in a straightened manner during the investigation. Immediately after the MRI was performed, the patient exhibited dystonic and ballistic movements of one leg. The symptoms gradually diminished over a period of weeks. One theoretical explanation for this event is that the MRI resulted in possible thermal lesioning within the right STN, even though this possibility was not demonstrated by CT-scanning due to artefacts. One possible mechanism for this type of
injury is that the straightened externalized wire might act like an antenna within the coil, affected by the oscillating electrical field\textsuperscript{89}.

The second case concerns a bilaterally implanted patient where the left IPG was placed in the abdominal wall, and the right IPG below the clavicle. The patient underwent a lumbar MRI with a 1-Tesla unit using a full body coil, which resulted in a thermal lesion of 2-3 cm in diameter and a small haemorrhage at the tip of the left intracerebral electrode, leaving the patient in a comatose state\textsuperscript{1,44,124,240}.

Based on our own experience as well as the reports in the literature\textsuperscript{89,238,292}, we have judged MRI, with standard settings (a send/receive head coil, a 1,5-Tesla unit and a specific absorption rate not exceeding 0.4 W/kg) to be safe to perform in patients who have DBS.

\textit{Electrocautery:} Monopolar electrocautery has been reported to create electrical shocks when the IPG is in the activated state\textsuperscript{300}, and this should be avoided, if possible. If it can not be avoided, we agree with Weaver et al\textsuperscript{300} that when contemplating the use of electrocautery, the IPG should be turned off before surgery, and the dispersive plate placed so that the electrical field would not cross the DBS-system. Bipolar electrocautery has not been reported to cause any adverse effects in this group of patients.

\textit{Diathermy:} None of our patients in our study have undergone treatment with diathermy, in accordance with the recommendations from Medtronic\textsuperscript{189}. Nutt et al\textsuperscript{210} reported one case where diathermy for 60 minutes in the maxilla after teeth extraction resulted in lesions around the STN-electrodes leading to a vegetative state in the patient. Medtronic has reported a second case where a vegetative state in a patient occurred after treatment of chronic scoliosis with diathermy\textsuperscript{189}.

\textit{ECG:} In patients who have DBS, artefacts may occur on the ECG which are caused by the stimulation, and which can potentially render the ECG uninterpretable. We
believe that it would be preferable for patients with DBS to deactivate their IPGs before undergoing ECG to avoid this stimulation interference with the interpretation of the ECG. In emergency situations where the patient cannot deactivate their IPG themselves, an uninterpretable ECG may of course complicate diagnosis/treatment of a heart condition, and thus constitute a risk for the patient.\textsuperscript{45,154,187}

Artefacts on ECG have been reported to occur during different forms of therapeutic electrical stimulation, including transcutaneous nerve stimulation, dorsal column stimulation and DBS.\textsuperscript{45,69,122,150,264,269} In DBS, this appears to occur only with monopolar stimulation, when the current passes from the electrode to the IPG at the chest. With bipolar stimulation, the current passes only between the contacts of the electrode.\textsuperscript{45}

Heart defibrillation: Even though none of the patients sustained any injury after heart defibrillation, Yamamoto et al.\textsuperscript{307} have reported one case where cardioversion in a patient with a radiofrequency receiver connected to an electrode in the thalamus resulted in a lesion surrounding the tip of the electrode. As in the case with electrocautery, it is recommended that the IPG voltage be set to zero, and then turned off before cardioversion. Furthermore, the pads of the defibrillator should be placed as far as possible away from the IPG.

Pacemakers: Modern pacemakers and ICDs sense electrical potentials related mostly to activity of cardiac cells, and are programmed to respond with an electrical discharge designed to treat a hazardous or malignant heart rhythm. Electrical discharges from other sources, including, for instance, DBS, can be sensed by the implanted cardiac device and be interpreted as a cardiac dysrythmia. Modern pacemakers, however, are equipped with filters which help to keep many forms of electrical non-cardiac signals from being identified as dysrhythmias. Interference that is not filtered out can potentially result in two different clinical problems. The most serious problem is when the above effect leads to inhibition of
pacemaker function, which might be deleterious to the patient. The interference might also give rise to a de-synchronisation of pacing function, a less dangerous but still undesired effect\textsuperscript{139}. In the patient with 3\textsuperscript{rd} degree AV-block, syncope after monopolar DBS was probably induced by an interference with the pacemaker resulting in inadvertent pacing inhibition and bradycardia.

DBS interference with ICD function can be caused either by an inhibition of defibrillator recognition and response to arrhythmia due to undercounting, or in an inappropriate discharge due to activation of the defibrillator function by electrical events which are not related to a ventricular arrhythmia\textsuperscript{249}. In our patient with the ICD, monopolar DBS appears to have caused repeated and frequent ICD discharge. No negative effects were seen when combining bipolar DBS with implanted cardiac devices.

With increasing use of pacemakers/ICDs and DBS, there will be more patients where both of these devices are present and activated. No complications have been reported previously, and to our knowledge only two cases has been reported concerning this subject, not counting three reports dealing with pacemakers and spinal cord stimulation\textsuperscript{6,139,212,247,249}.

In order for the combination of DBS and cardiac pacemakers/defibrillators to be safe, the following points should be taken into consideration.

- A cardiologist should be consulted before implantation of a DBS system in a patient with cardiac pacemaker/defibrillator. The purpose of this consultation is to identify possible risks, and, if warranted, optimize the settings of the implanted cardiac device.
- If possible, bipolar DBS should be used. If monopolar stimulation is necessary, the patient should remain hospitalised and under observation during the day of programming or reprogramming. A cardiologist and the DBS-responsible physician should rule out interference with the function of the pacemaker/defibrillator.
• A hand-held patient programmer should be used for the DBS instead of a magnet, since magnets have the potential of also negatively affecting an implanted cardiac device\textsuperscript{249}.

• When possible, the ICD should be placed in such a position that the vector of discharge be kept away from the IPG\textsuperscript{249}.

When comparing DBS and lesioning there are some evident disadvantages associated with the former method. DBS is considerably more costly than lesioning, and the IPG has to be replaced at intervals of approximately 4-7 years. The length of surgery for DBS was considerably longer than for lesioning. The implantation of the connection cable and the IPG was done under general anaesthesia, while lesioning is done under local anaesthesia. DBS is more laborious than lesioning, necessitating continuous follow up with repeated visits for optimising of stimulation parameters. Further, the risk for hardware related complication is not insignificant. However, it is obvious that DBS has some major advantages compared with lesioning, especially in thalamic surgery. The literature on subthalamotomies is limited\textsuperscript{4,98,179,228}, and considering the frequent reports on dysarthrophonia and psychiatric side-effects after STN-DBS, it seems unlikely that lesion of the subthalamic nucleus, especially bilaterally, would be an attractive alternative to DBS.

Concerning pallidal surgery our material could not demonstrate any advantages of DBS as compared to lesioning, nor has it been demonstrated in the literature that unilateral pallidal DBS is superior to pallidotomy, neither concerning risks, nor concerning efficacy. The question of efficacy of pallidotomy vs. pallidal DBS will be further discussed based on the findings in paper VI.
Paper V

In paper V, five patients were operated on first with unilateral pallidotomy then with contralateral pallidal DBS. It was demonstrated that the effect of pallidotomy was more robust than the effect of DBS, on contralateral appendicular symptoms and signs, especially dyskinesias. This was despite the fact that the initial pre-operative scores for the side contralateral to the pallidotomy were worse than for the side contralateral to DBS. Also, the effect of the lesions was evaluated 37 months after surgery, as compared with 22 months after DBS. These seemingly paradoxical results may be consistent with what has been reported empirically by others (Lozano, 14th international congress on Parkinson’s disease and related disorders, Helsinki, August 2001. Kelly, International workshop on functional neurosurgery for movement disorders, pain and psychiatric illness, London, November 2004) where with a staged bilateral pallidotomy, the first side operated usually results in a more pronounced improvement, compared to the last operated side. The better effect of the pallidotomies, relative to pallidal DBS, might therefore not be a consequence of the method, but instead due to the fact that the first operated side in a staged procedure shows a more marked improvement, regardless of the chosen method.

The short-term outcome of pallidotomy3,55,60,62-64,74,90,137,170,173,284 as well as of pallidal DBS14,67,87,175,177,267,268,305 has been reported to be favourable. Concerning the long-time effects the literature is scarce. The natural progression of Parkinson’s disease in combination with aging of the patient makes interpretation of long-time follow-up complicated, as shown in a publication on ten years follow-up of pallidotomies114. A “sustained” but to varying degree diminished benefit has been reported up to four years after lesional surgery12,70,76,78,224,296. For pallidal DBS a number of small studies presents a follow-up of two years or more68,91,103,183,303. Bilateral surgery has been documented in a limited number of pallidotomies55,64,74,90,137,191,284, pallidal DBS67,68,87,175,177,305, and DBS combined
with a contralateral pallidotomy\textsuperscript{88,191}. The differences between materials, length of follow-up, methods and presentation of the results makes a comparison between studies of pallidotomies and pallidal DBS virtually impossible. The few studies comparing the effect of pallidotomy and DBS have shown a fairly equivalent outcome\textsuperscript{167,190}.

Adverse effects were only present after the contralateral DBS procedure. The negative effect on speech in three patients, secondary to the DBS, should probably not be attributed to the DBS technique, but rather to the bilaterality of surgery. The presence of a stereotactic pallidal lesion on one side \textit{per se} may have predisposed the patients for higher risk of speech problems following the contralateral DBS. Multiple studies suggests that the rate of adverse effects is clearly higher for bilateral pallidotomies\textsuperscript{55,64,74,90,137,191,226}. The fact that dysarthria in two patients was partly reversible with adaptation of the stimulation settings shows the major advantage of DBS. It is notable that not all side effects are reversible after DBS, as the case with hypophonia demonstrates. This patient had a pre-existing hypophonia, that was not aggravated by the pallidotomy, but which deteriorated after the subsequent pallidal DBS. One possible explanation for this might be the micro-pallidotomy that is caused by the mere introduction of the electrode into the pallidum since this patient already had a pallidal lesion contralaterally. The number of transient complications in other studies related to unilateral pallidotomy has been reported to be 7.9\% - 69.2\% of the patients, and permanent complications between zero and 19.2\%\textsuperscript{56,60-63,170}. The frequency of complications reported for bilateral pallidotomies was reported to be much higher compared with unilateral procedures\textsuperscript{55,61,64,90,135,137,191,259,284}. However, concerning reports of complications secondary to pallidal DBS, we found three studies with a total of 53 bilateral and 10 unilateral pallidal DBS procedures with an complication-frequency ranging from 12.5\% to 144.4\%\textsuperscript{87,177,183}.

DBS is considerably more costly than lesioning, and the neurostimulator has to be replaced at intervals of approximately 3-6 years. Further, the rate of hardware-related
complications has been reported to occur in up to 49% \(^{23,146,157,182,213,295}\). While the rate of complications can be regarded as stable after the first postoperative months after a pallidotomy, the opposite is true for pallidal DBS, where the risk of accumulated adverse events is likely to increase with time. This stresses the necessity of long-time evaluation when comparing lesional surgery and DBS. In our material, four additional operations were warranted due to various problems with the implanted devices. Further, DBS is more laborious process than pallidotomy, necessitating continuous follow up and repeated visits for optimising of stimulation parameters.

The excellent results of STN-DBS have led to this procedure becoming the treatment of choice in advanced Parkinson’s disease \(^{81,125,140,152,153,158,161,169,218,219,255,297,301,302}\). Still, we still prefer pallidal surgery in PD patients where dyskinesias or dystonia are the dominating symptoms, especially if unilateral, and in patients not suitable for STN DBS due to age older than 70 years, depressive symptoms, hallucinations, mild cognitive deficits, or impaired balance. From the material presented here, and from our previous experience, we consider the effect of pallidotomy to be at least as good and as safe as that of pallidal DBS. Since the risks of adverse events increase after bilateral surgery \(^{55,61,64,90,135,137,191,259,284}\), and since these might be at least partly reversible with stimulation, we can consider performing unilateral pallidotomy on the most affected side, and if needed, combining with pallidal DBS on the contralateral side.

The major methodological default of the present study is that all patients had a pallidotomy first and a pallidal DBS subsequently. Perhaps the results would not have been the same if the order of surgery had been reversed.
**Paper VI**

*Efficacy*

The contralateral hand showed no tremor progression off stimulation during the follow-up period. The significant increase in the total ETRS off stimulation was caused by an increased tremor in the ipsilateral hand, and by a deterioration of the ADL. The increase of tremor in the ipsilateral hand is considered as a natural progression of the disease. A similar increase was not seen contralateral to DBS, even though several of the patients, judged by our clinical evaluation, have shown a progression of tremor. This progression was however not demonstrated in the ETRS, because of a ceiling effect of the ETRS, since these patients already at baseline scored the highest values on these items.

The decline of ADL-ability from baseline to the last evaluation might be due to progression of the disease, both at the treated and the non-treated side. The patients had reached a mean age of 75 years at the time of this evaluation, and it is possible that normal aging and co-morbidities might be partly responsible for declines in ADL score. These comorbidities include dementia, normal pressure hydrocephalus, severe chronic obstructive lung-disease, visual impairment, rheumatoid arthritis, arthrosis, extremity fractures and arthrodesis, etc.

DBS provided a substantial reduction of tremor of the contralateral hand when compared to baseline and to the off condition at both evaluations. There was however a significant reduction over time of effect between the two evaluations, as observed in items 11-14 and 5/6 (mainly concerning action tremor) for the contralateral hand. Thus, while the effect on resting tremor and postural tremor showed little change, tremor of activity was less stable over time. This distinction is relevant since the patients ADL’s are typically much more affected by tremor of activity.
Stimulation parameters

The pulse effective voltage was 0.20 V after one year, 0.24 V after 3 and 5 years and 0.29 V after 7 years. This can be compared with results from Rehncrona et al, with 0.29 V after 2 years and 0.26 V after 6-7 years, Sydow et al 0.27 V after 1 year and 0.32 V after 6 years, Putzke et al 0.38 V after one year and 0.37 V after 3 years and Koller et al 0.35 V at 1 year and 0.46 V after 3 years. It is difficult to interpret the differences concerning stimulation-strength and its increase over time between the different studies. Sydow et al suggested that the lower stimulation amplitude in their material, as compared with the results of Koller et al, might be due to more optimal positioning of the electrodes. It is also possible that lower stimulation amplitude might reflect a placement where stimulation-induced side-effects are reached at a relatively lower level, thus preventing an increase of amplitude, even though this might be needed for more tremor-reducing effect. The question of electrode-position in relation to the optimal target site cannot solely be based on the amplitude, but rather the combination of the different effects of stimulation, including side effects. Similarly, a lack of increased stimulation strength over time does not necessarily imply a lack of increase of tremor, or a lack of need for increased stimulation strength. It is possible that in some patients the stimulation strength cannot be increased further without eliciting intolerable side-effects.

Development of tolerance after Vim-DBS is well known. It is likely that most of the increase of stimulation strength seen during the follow-up period was the result of tolerance, even though progression of disease might be a contributing factor. When tolerance occurs, increasing stimulation strength often cannot be performed without inducing unacceptable side effects, thus leading to a loss of effect.
The increased use of bipolar stimulation over time is interpreted as a consequence of development of tolerance/disease-progression to a level where monopolar stimulation cannot be increased further without eliciting side effects.
GENERAL SUMMARY

Unilateral lesional surgery, by itself, does not harbour more perioperative complications than DBS. Side effects of lesioning are sometimes reversible, and complications of DBS are sometimes irreversible.

DBS has a disadvantage in its higher cost, more complicated surgery, life-long follow-up and the constant risk of hardware-related complications. The implanted foreign materials are under constant risk of causing or suffering damage. The often long time period between surgery and complication means there is a strong indication for long-term follow-up. Several of the potential hardware-related complications seem to be avoidable with increased surgical experience.

DBS systems are subject to and sometimes adversely affected by electromagnetic forces in the environment. These outside electromagnetic forces do not normally constitute a serious clinical problem, and can be easily managed by the patient. In rare cases, this exposure can constitute a severe threat to the well-being of the patient, and has in a few reported cases resulted in severe neurological impairment. MRI and cardiac pacemakers/defibrillators seem to be safe in patients with DBS provided that some precautions are taken. Side effects of electromagnetic influences should to some extent be avoidable with well-informed patients as well as preferential use of the magnetically shielded Kinetra and the patient programmer.

Every brain-target should be evaluated concerning the relative risk and benefit of the different surgical methods, and whether the surgery is uni- or bilateral.

The experience concerning subthalamotomies is limited, and the rather high frequency of cognitive and psychiatric side effects associated with STN-DBS, makes irreversible lesioning seems to be a less desirable alternative.
Concerning pallidotomy, the efficacy on the parkinsonian symptoms, especially dyskinesias, rigidity and tremor, was more pronounced than for pallidal DBS, despite numerous postoperative patient visits to optimise stimulation parameters. The better effect of the pallidotomy might however not be due to the method itself, but to the order in which the staged procedures were performed in this study.

Pallidal DBS did not have fewer complications than pallidotomy, nor did use of pallidal DBS instead of pallidotomy, contralateral to a previous pallidotomy, protect from risk of dysarthria and dysphonia. Unilateral pallidotomy is therefore an alternative to pallidal DBS, especially for patients with mainly unilateral symptoms. For bilateral pallidal procedures, either a combination of pallidotomy and pallidal DBS, or bilateral pallidal DBS might be considered.

The side effects of thalamotomy are so frequent that Vim-DBS must be preferred. Vim-DBS is an efficient and safe treatment for essential tremor that can provide many years of symptom relief. There is a diminishing effect over time, most noticeable concerning tremor of activity. Development of tolerance, and probably the natural progression of the disease, typically leads to a need for increasing the strength of stimulation.
CONCLUSIONS

1. Unilateral lesional surgery, by itself, does not have more perioperative complications than DBS.

2. DBS has some disadvantages including its higher cost, more complicated surgery, life-long follow up and the constant risk of hardware-related complications.

3. Several of the potential hardware-related complications probably can be reduced with increased surgical experience.

4. DBS systems are quite frequently being affected by electromagnetic forces in the environment, which in rare cases might constitute a threat to the patient.

5. To minimize the risks related to electromagnetic interference, preferential use of the magnetically shielded Kinetra, with a disabled magnet mode, should be considered, and every patient should be equipped with a patient programmer.

6. Every brain-target should be evaluated concerning risk-benefit balance for the different surgical methods, and whether the surgery is uni- or bilateral.

7. The experience concerning subthalamotomies is very limited, and therefore at present, DBS is the method of choice for this target.

8. STN-DBS has in some cases resulted in alterations of mood, cognitive functions and behaviour, and it seems likely that the STN and its vicinity has some psycho-modulating properties, which stresses the importance of proper selection of patients for this procedure.

9. The effect of unilateral pallidal DBS is not better than for unilateral pallidotomy, nor does DBS have any advantages concerning complications as compared to lesioning in the pallidum. Pallidotomy is therefore an alternative.
to pallidal DBS especially for patients with mainly unilateral symptoms. For bilateral pallidal procedures, either a combination of pallidotomy and pallidal DBS, or bilateral pallidal DBS might be considered.

10. The side effects of ventrolateral thalamotomy for tremor are so frequent that Vim-DBS must be preferred.

11. Vim-DBS is an efficient and safe treatment for essential tremor that can provide many years of symptom relief. There is a diminishing effect over time, most noticeable concerning tremor of activity.
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