Deep Brain Stimulation of the Posterior Subthalamic Area in the Treatment of Movement Disorders

Anders Fytagoridis

Department of Pharmacology and Clinical Neuroscience, Neurosurgery
Umeå University, Umeå, Sweden
ISBN: 978-91-7459-328-0.
ISSN: 0346-6612
Umeå University Medical Dissertations,
New Series No. 1464

Responsible publisher under Swedish law: Dean of the Medical Faculty

Umeå University Medical Dissertations, New Series No. 1464
ISBN: 978-91-7459-328-0.
ISSN: 0346-6612
Cover image, front: Mattias Åström
Printed by: Print & Media, Umeå University
Umeå, Sweden 2012

I would like to remind younger readers of Lars Leksell's policy: read and think more, write less, and write only about the important findings

- Lauri Laitinen, in "Personal memories of the history of stereotactic neurosurgery." [2]

I dedicate this thesis to the memory of my late grandparents, Bror Olof, Alfa, Giannis, and Anastasia. I also dedicate this work to my beloved wife, Isa Gustin, who always knows what's best for me, especially when I have forgotten it myself.

Anders Fytagoridis, Umeå, December, 2011

Table of Contents

Abstract

Background: The posterior subthalamic area (PSA) is essentially composed of the caudal Zona incerta and the prelemniscal radiation. Subthalamotomy in the PSA was renowned for its effectiveness in alleviating movement disorders and particularly tremor. The modern literature on DBS of this area is limited, but promising results have been presented for Parkinson's disease (PD), essential tremor (ET) and other movement disorders.

Aim: To evaluate the safety of PSA DBS with emphasis on the panorama of side effects, the distribution of stimulation-induced side effects and the effects of PSA DBS on verbal fluency. To evaluate the therapeutic effect of PSA DBS on less common forms of tremor, tremor-dominant PD, and concerning the long-term results in ET.

Method: 40 patients were evaluated regarding side effects of the procedure. 28 patients with ET were analyzed for stimulation-induced side effects in a standardized manner. The locations of the contacts that caused stimulation-induced side effects were plotted on atlas slides. A 3-D model of the area was created based on these slides. Verbal fluency was analyzed in 17 patients with ET before surgery, after 3 days and finally after 1 year. Five patients with less common forms of tremor and 18 with ET were evaluated according to the ETRS at baseline and one year or 3-5 years after surgery, respectively. 14 patients with mainly unilateral tremor-dominant PD were evaluated a mean of 18 months after surgery according to the motor part of UPDRS.

Results: PSA DBS was associated with few serious side-effects, but a transient and mild postoperative dysphasia was found in 22.5% of the patients. There was a slight transient decline in the performance on verbal fluency tests immediately after surgery. Visualization of the contacts causing stimulation-induced side effects showed that identical responses can be elicited from various points in the PSA and its vicinity. The effect on the less common forms of tremor was excellent except for neuropathic tremor where the effect was moderate. A pronounced and sustained microlesional effect was seen for some of the patients. After a mean of 4 years with unilateral PSA DBS the total ETRS score was improved by 52.4%, tremor by 91.8% and hand function by 78.0% in the patients with ET. There was no increase in the stimulation strength over time. In PD, the scores improved 47.7% for contralateral UPDRS III. Contralateral tremor, rigidity, and bradykinesia improved by 82.2%, 34.3%, and 26.7%, respectively.

Conclusions: PSA DBS generally seem to be a safe procedure, but it may be associated with transient declines of verbal fluency. There was no clear somatotopic pattern with regard to stimulation-induced side effects in the PSA. PSA DBS can alleviate tremor regardless of the etiology. The long-term effects in ET were favorable when compared to our previous results of Vim DBS. The effect on Parkinsonian tremor was satisfying, however, the reductions of rigidity and bradykinesia were less compared to previous studies of PSA DBS for PD.

Keywords: Deep brain stimulation, Movement disorders, Posterior subthalamic area, Zona incerta, Prelemniscal radiations, Tremor, Essential tremor, Parkinson`s disease.

Manuscripts

I. Complications and Side effects of Deep Brain Stimulation in the Posterior Subthalamic Area
Fytagoridis A., Blomstedt P.
Stereotact Funct Neurosurg 2010; 88:88–93

II. Stimulation-induced Side Effects in the Posterior Subthalamic Area: distribution, characteristics and visualization
Fytagoridis A, Åström M, Wårdel K, Blomstedt P.
Manuscript, under revision

III. Effects of Deep Brain Stimulation in the caudal Zona incerta on Verbal fluency
Fytagoridis A, Sjöberg R, Fredricks A, Nyberg L, Blomstedt P.
Manuscript, submitted for publication

IV. Deep Brain Stimulation in the Posterior Subthalamic Area in the Treatment of Tremor
Blomstedt P, Fytagoridis A, Tisch S.
Acta Neurochirurgica. 2009; 151(1):31-6.

V. Long-term follow-up of Deep Brain Stimulation of the caudal Zona incerta for Essential tremor
Fytagoridis A, Sandvik U, Åström M, Bergenheim T, Blomstedt P.
J Neurol Neurosurg Psychiatry 2011; doi:10.1136/jnnp-2011-300765 (E-pub ahead of print).

VI. Unilateral caudal Zona incerta Deep Brain Stimulation for Parkinsonian tremor
Blomstedt P, Fytagoridis A, Linder J, Forsgren L, Hariz M.
Manuscript, submitted for publication

Populärvetenskaplig sammanfattning på svenska

Neurologiska rörelsestörningar såsom Parkinsons sjukdom, essentiell tremor och dystoni kan leda till nedsatt livskvalitet och nedsatt förmåga att självständigt klara av vardagliga sysslor.. När läkemedel inte ger tillräcklig lindring av symtomen kan stereotaktisk funktionell neurokirurgi vara en alternativ behandlingsmetod. Med hjälp av stereotaktisk teknik kan man med millimeterprecision nå djupa strukturer i hjärnan såsom nervkärnor och nervfibrer. Vid neurologiska rörelsestörningar används metoden i dagens läge i huvudsak till att inplantera stimuleringselektroder djupt i hjärnan, s.k. Deep Brain Stimulation (DBS) eller fritt översatt ”djup hjärnstimulering”. Metoden används mestadels för att med hjälp av stimulering kunna reducera skakningar (tremor), ofrivilliga rörelser, krampartade kroppsställningar samt vad gäller Parkinsons sjudom även stelhet och långsamma rörelser.

I denna avhandling med namnet ”Deep brain stimulation of the posterior subthalamic area in the treatment of movement disorders”, har DBS i det bakre subthalama området (engelska: posterior subthalamic area, PSA) utvärderats för rörelsestörningar där handikappande tremor är en gemensam nämnare. Området är tätt packat med nervfibrer och nervkärnor som inverkar i kontrollen av våra rörelser. Redan under 60-talet var området känt som ett effektivt mål för att lindra rörelsestörningar och framförallt tremor, men de moderna studierna av DBS i detta område är relativt få.

Säkerhetsaspekterna är ytterst viktiga eftersom DBS i dagens läge oftast inte botar, utan syftar till att ge betydande lindring av patientens symtom. Relativt lite kunskap finns i dagens läge om eventuella biverkningar av just PSA DBS. I arbete 1-3 utvärderades olika säkerhetsaspekter av DBS i PSA. Studie 1 undersökte förekomsten av biverkningar hos patienter opererade med DBS i PSA. Målet befanns vara säkert och förenat med få allvarliga biverkningar. Några fall av övergående svårighet att hitta ord upptäcktes. Detta har inte rapporterats tidigare efter PSA DBS, men däremot efter operationer av närliggande mål i hjärnan.

Studie 2 undersökte biverkningar orsakade av själva stimuleringen. Samma typ av biverkning kunde utlösas av flera olika strukturer i området.

Studie 3 byggde vidare på det första arbetet och undersökte närmare den övergående svårigheten att finna ord. Genom att testa ordflödet hos opererade patienter fann man att det fanns en övergående påverkan efter operationen. Det här berodde inte på om stimuleringen var av- eller påslagen och påverkade inte patienternas funktionsnivå.

Studie 4-6 utvärderade den kliniska effekten av PSA DBS för ett antal rörelsestörningar där tremor är ett dominerande symtom. Studie 4 studerade fem patienter med mer ovanliga former av tremor . Patienternas tremor lindrades väl. Effekten var god även mot smärtor och krampande muskler hos två patienter med s.k. dyston tremor.

I studie 5 studerades effekten av PSA DBS efter fyra år hos 18 patienter med Essentiell tremor (ET). En DBS operation innebär ofta en livslång behandling och det här gör att långtidsresultaten är ytterst viktiga. Behandlingen visade sig ha bibehållen effektivitet även på långsikt. Resultaten var fördelaktiga i jämförelse med långtidsstudier av DBS i thalamus. Thalamus är en kärna i hjärnan som i dagsläget är det mest vanliga målet för DBS vid ET.

I studie 6 studerades effekten av PSA DBS hos 14 patienter med Parkinsons sjukdom. Patienterna hade huvudsakligen ensidiga symtom som dominerades av tremor. Effekten mot tremor var god och jämförbar med tidigare studier. Effekten mot stelhet och långsamma rörelser var något mindre positiv. Vad detta beror på behöver studeras ytterligare. Sammanfattningsvis tyder avhandlingens resultat på att det bakre subthalama området (PSA) är ett säkert och effektivt mål för djup hjärnstimulering mot rörelsestörningar. Fler studier behövs för att klargöra om PSA är ett lämpligt alternativ i jämförelse med andra stereotaktiska mål.

Abbreviations

ADL, activities of daily living
AC, anterior commissure
CT, cerebellar tremor
CT, computed tomography
cZi, caudal zona incerta
DBS, deep brain stimulation
DT, Dystonic tremor
ET, essential tremor
ETRS, Essential Tremor Rating Scale
Fct, fasciculus cerebellothalamicus
GABA, γ-aminobutyric acid
Gp, globus pallidus
Gpe, globus pallidus externus
Gpi, globus pallidus internus
H, field H of Forel
H1, field H1 of Forel
H2, field H2 of Forel
HFS, high frequency stimulation
Hz, hertz
ICL, intercommissural line
IO, inferior olive
IPG, implantable pulse-generator
MCP, midcommissural point
Ml, medial lemniscus
MRI, magnetic resonance imaging
MS, multiple sclerosis
MPTP-monkey, monkey lesioned with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MRF, medial reticular formation.
NT, neuropathic tremor
PC, posterior commissure
PEV, pulse effective voltage
PD, Parkinson's disease
Ppn, pedunculopontine nucleus
PSA, posterior subthalamic area
PW, pulse-width
Raprl, prelemniscal radiation
RN, red nucleus
STN, nucleus subthalamicus
U, voltage
UPDRS, Unified Parkinson`s Disease Rating Scale
UPDRS, III Unified Parkinson`s Disease Rating Scale – Motor part
V, volts
Vim, nucleus ventralis intermedius thalami
VL, ventral lateral nucleus of thalamus
VLp, nucleus ventralis lateralis posterior thalami
Voi, nucleus ventrooralis interna thalami
Vop nucleus ventrooralis posterior thalami
WT, writing tremor
Zi, zona incerta
μs, micro-second

"Young man, they can beat and rob you of everything, but you will always keep your education."

– Matti, retired Finnish sailor giving the 19-year-old author advice about what to do in life. Gothenburg, Sweden, 2000.

Introduction

General Introduction

"*Dr. Ernest A. Spiegel held the belief that there is nothing that appears in the literature without some precedent in an older article."*

- Philip L. Gildenberg.[4]

The title of this thesis implies that it concerns deep brain stimulation (DBS). DBS signifies stimulation of subcortical structures for therapeutic purposes and the procedure is incorporated into the field of functional and stereotactic neurosurgery. The term functional neurosurgery implies a surgical procedure in the nervous system that aims at reducing symptoms and/or restoring function by in some way altering a dysfunction in the nervous system. The term stereotactic consists of the Greek word "stereo", meaning solid or three-dimensional in combination with –tactic, which is derived from the Latin word tactus (to touch) or can just be a linguistic evolution of the Greek word "taxis" (arrangement, order).[5, 6] Either way, by applying a three-dimensional reference system (the stereotactic frame) to the patient, we are able during functional stereotactic procedures to reach and affect structures deep in the brain through a small burr hole. Today, many consider stereotactic functional neurosurgery to be more or less the same as DBS, which normally is considered to have been introduced by Benabid et al. in 1987.[7] However, everything comes from something and "history often repeats itself," as Gildenberg stated in an article with the same name.[4] I personally feel that this is one of the key factors to the background of this thesis, history does repeat itself and a knowledge of history is essential for understanding the somewhat "back and forth" evolution that eventually led us to conduct the studies in this thesis concerning DBS in the posterior subthalamic area (PSA).[3]

A simplified outline of the history of stereotactic neurosurgery and the surgical procedures for movement disorders will therefore be included in this introduction.

Historical background

The French Philosopher René Descartes (1596–1650) is accredited for the introduction of the Cartesian coordinate system which can be said to constitute the "foundation" of stereotactic surgery. By defining an origo, or 0, and a scale that may have positive as well as negative values, it is possible to identify any point in space with this coordinate system using three intersecting planes at right angles (Figure 1). Several constructions for guiding intracranial procedures had predated the publication in 1908 of the "Horsley-Clarke stereotaxic frame" for use in animals. However, this frame is generally regarded as the first one based on Cartesian coordinates and is therefore also regarded as the predecessor of the current stereotactic systems for humans.[8-14] Though the first frame for human stereotaxy actually had been constructed before, it was not until 1947 when Spiegel and Wycis presented their "stereotaxic apparatus for operations on the human brain" that the technique really took off.[10, 13, 15, 16] The rapid spread of this technique from this point was certainly due

to numerous reasons. The ability to use intraoperative x-ray which facilitated the use of intracranial landmarks was fundamental, but probably most importantly: there simply was a great need to develop the method.[2, 17-19]

The initial purpose of Spiegel and Wycis was to provide a safer alternative to prefrontal lobotomy for psychiatric disease; however, the method would predominately spread in the field of surgery for movement disorders, mainly because there were no effective medical alternatives at that time.[2, 4, 15, 20-24] Since the beginning of the 20th century surgeons had tried different open intracranial operations on the motor cortex or its descending pyramidal pathways in order to alleviate symptoms as involuntary movements and tremor.[9, 24-30] These procedures were usually associated with hemiparesis and high mortality, and the concept of targeting instead the extra pyramidal motor system, such as the basal ganglia, had not been considered previously as an option.[17, 30-32]

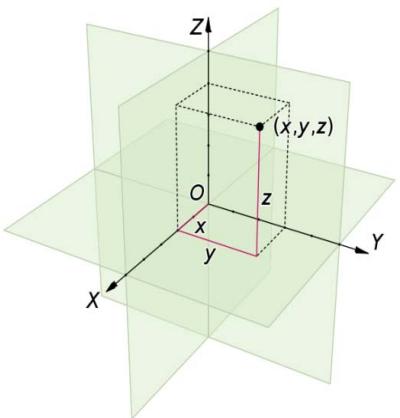


Figure 1) Schematic drawing of a Cartesian 3D coordinate system. (*Reproduced with kind permission from the publishers.*[1])

However, during the 1940s and 1950s interventions aimed at structures of the basal ganglia, such as the caudate nucleus and the globus pallidus (Gp), proved that surgical lesions of the extra pyramidal motor system could lessen symptoms of movement disorders without simultaneously causing hemiparesis.[24, 30, 33-41] These operations were, however, also limited in their popularity due to high risks and low predictability of the outcome.[17, 28, 30, 34, 38, 42]

Inspired by the pioneer work of Spiegel and Wycis, numerous neurosurgeons soon constructed their own stereotactic frames which were used at different centers around the world.[17, 43-56] Lars Leksell presented his first frame in 1949, which already had the movable semicircle that still is the hallmark of the later model which was used for the operations in this thesis.[52, 57] With the use of stereotaxy, the mortality quite rapidly sank under 1% and, for the first time in history, there was a safe and effective way to ease the burden on the patients with movement disorders in general and PD in particular.[24, 58-60] By using the stereotactic frame, the surgeon was able to insert a thin cannula or an electrode into central structures of the brain and make therapeutic lesions with millimeter precision. The lesions were mostly made using radiofrequency, electro-, thermo- or chemocoagulation.[26, 61] The first widely used target for stereotactic lesions in PD was the globus pallidus and hence the procedure was named pallidotomy. In 1954 Hassler presented the ventral thalamotomy, which was advocated due to its superior effect on tremor and therefore surpassed pallidotomy in popularity.[38, 62-65] Further evolution led to the development of campotomy and later also the subthalamotomy, which was a lesion below the thalamus in the zona incerta (Zi) and the fiber tracts of the subthalamic area.[3, 66-70] The first publication on subthalamotomy was by Wertheimer et al. in 1960 and the procedure was preferred by some surgeons as they considered it even more potent in alleviating tremor than thalamotomy.[71] Since L-dopa was not in use back then, the PD patients of that era were in an earlier, but equally severe, state of the disease compared to the patients who are candidates for surgery today. The predominant indications for surgery were therefore tremor and rigidity, and not bradykinesia and

dyskinesias.[17, 24, 59, 64, 72, 73] By 1965 approximately 25,000 stereotactic procedures for Parkinsonism had been performed.[17] A dramatic turnaround of events occurred around 1968 when effective L-dopa preparations became widely available and revolutionized the management of patients with PD.[17, 38, 74-77] For the first time, there was an effective pharmacological treatment for PD and the need for stereotactic surgery was now considered small.[77, 78] What often is referred to as the "lesional era" of stereotactic neurosurgery had passed its peak and during the 1970s and 1980s only certain centers still performed stereotactic functional procedures for movement disorders.[3, 17, 19, 78] It would take approximately 20 years before there once again was a general awareness of the need for stereotactic surgery for patients with PD and other movement disorders. This second turnaround in history is often referred to as the "renaissance" of functional stereotactic neurosurgery. Precisely as in the 1950s, there was once again a massive eruption of activity in the field, clinically as well as scientifically. The development was spurred by the seminal paper by Laitinen et al. in 1992 that revived the advantageous effects of Leksell`s posteroventral pallidotomy on the troublesome motor symptoms of PD, which at this time in history, apart from tremor and rigidity, were also bradykinesia and L-dopa-induced dyskinesias.[19, 65, 79] Development in the field of surgery for movement disorders was further spurred by the introduction of the use of high-frequency stimulation of the ventrolateral thalamus (Vim DBS) and subthalamic nucleus (STN DBS) initiated by the Grenoble group, as well as the introduction of internal globus pallidus (Gpi) DBS by Siegfried et al.[7, 80-105] DBS soon replaced lesional procedures almost entirely since similar therapeutic effects could be achieved from the same brain targets in a "reversible manner" and hopefully also be associated with fewer complications.[106-116] At present, in the midst of the "modern era" of DBS, an estimated over 80,000 DBS procedures have been performed worldwide in the treatment of movement disorders.[117] STN DBS is most often preferred in PD due to its effects on tremor, rigidity, and bradykinesia, as well as its ability to reduce L-dopa medication.[81, 83, 97] Vim DBS is mainly used for tremor-dominant disorders and Gpi DBS mainly for dystonia and some cases of PD.[3, 80, 100, 102, 118-124]

DBS has generally been applied to targets that were previously used to perform lesions. Subthalamotomy was, as mentioned above, considered to be an effective procedure for the alleviation of movement disorders with tremor.[3, 22, 66, 68-70, 125-140] The targets for this procedure during the lesional era appear to have mainly been either the Zi or the prelemniscal radiations (Raprl), which in this thesis is incorporated into the term PSA.[3, 66, 128, 134] Of course, previous to the development of MRI and CT, it was difficult to confirm the anatomical location of a lesion by other means than an autopsy. The reports of DBS of these structures during the "modern era" have been very limited, even to the extent that it has been referred to as a "forgotten target".[3, 22, 126, 141]

"Though we should not refuse to give modern authors due credit for their discoveries or happy imitations, it is none the less just to restore to the ancients what properly belongs to them."

- Ceslus, Liber Medicinae Secundus, Cap XIV

The Posterior Subthalamic Area

The PSA is bounded superiorly by the nuclei of the ventral thalamus and inferiorly by the superior margin of the substantia nigra. It lies posterior of the STN and anterior of the medial lemniscus. Medially, it is outlined by the lateral margin of the red nucleus (RN) and the lateral border is made up of the STN and more posteriorly of the posterior limb of the internal capsule (Figure 2). The primary component structures are the Zi and the Raprl. The areas often designated as the fields of Forel (H, H1 & H2) lie more anterior and are not components of the PSA. It should be noted that there is no exact definition of the PSA which is generally agreed on. The Zi and the Raprl will be discussed in more detail below.[3, 126, 141-143]

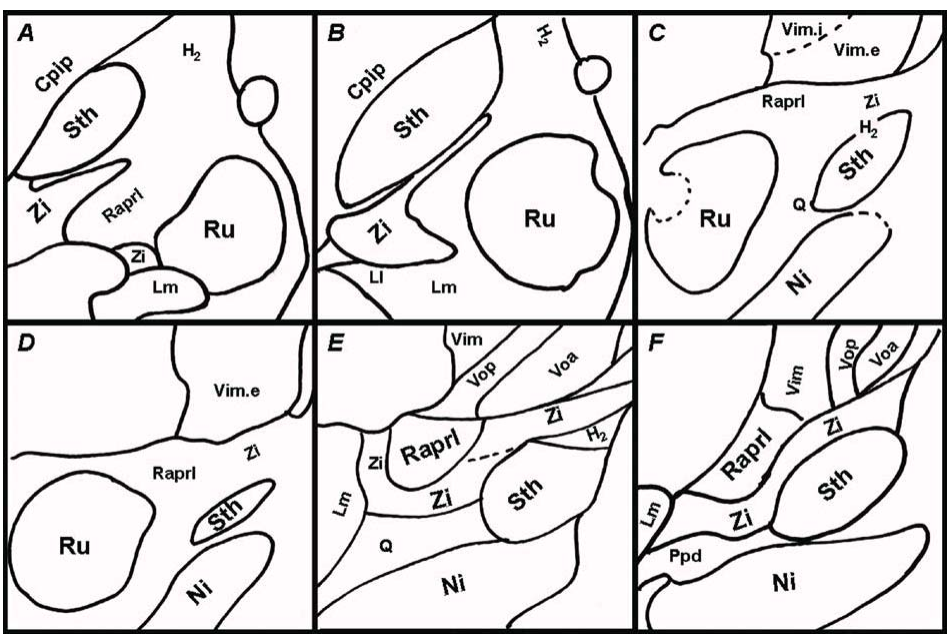


Figure 2) Schematic drawing based on the atlas of Schaltenbrand & Wahren demonstrating selected structures in the posterior subthalamic area and its surroundings. A & B corresponding to horizontal slice H.v -1.5 & -3.5, respectively. C & D corresponding to coronal slice F.p 5.0 & 7.0, respectively. E & F corresponding to sagittal slice S.I 10.5 & 13.0, respectively.

(Cpip; Internal capsule, posterior limb; H2: Field H2 of Forel; Sth: Subthalamic nucleus; Ll: Lateral lemniscus; Lm: Medial lemniscus; Ni: Substantia nigra; Ppd: Peripeduncular nucleus; Q: Fasciculus Q; Raprl: Prelemniscal radiation; Ru: Red nucleus; Vim: Nucleus ventralis intermedius of thalamus; Vim.e: External nucleus ventralis intermedius of thalamus; Vim.i: Internal nucleus ventralis intermedius thalami; Voa: Nucleus ventrooralis anterior thalami; Vop: Nucleus ventrooralis posterior thalami; Zi: Zona incerta.)
(Reprinted with kind permission from the publishers.[3])

Subthalamotomy

The target for the subthalamotomy during the "lesional era" was not the subthalamic nucleus as the term often signifies in more modern literature.[144-149] Even though modern studies have indicated that there isn't an absolute correlation, lesions of the STN (or nucleus of Luys) were not intentionally performed since surgeons feared that this would cause contralateral hemiballism as had been observed in stroke patients.[144-154] Several groups explored the subthalamic area during the lesional era. Spiegel and Wycis performed what they called a "campotomy", which name signified that it was a lesion of the "campus Foreli" or fields of Forel.[16, 155, 156] Accordingly, these lesions were produced somewhat anterior to the PSA. Meyers, and also other surgeons, performed subthalamic lesions in the substantia nigra (substantia nigrotomy/-lysis).[21, 26, 31, 155, 157, 158]

Exactly why and how the posterior subthalamic area was discovered as a target is somewhat hard to tell from the literature. The proximal location of the PSA, just inferior to the ventrolateral thalamus, might be fundamental in this aspect. The PSA can, in fact, often be reached by using a standard trajectory from a frontal burr hole and by just advancing the electrode a few millimeters inferior to the thalamus (i.e. below the intercommissural line, (ICL)).[3, 159, 160] It was from early on noted that a pronounced microlesional effect was characteristic of the area. A marked reduction of tremor is often observed just by entering the target area with an electrode. It was further claimed that a smaller lesion of the subthalamic area could be as effective as a larger thalamic lesion.[3, 68-70, 137, 153, 161-166] Consequently, regardless of whether the PSA was reached on purpose or not, the pronounced microtomy effect probably encouraged surgeons to explore the area further since alleviation of tremor was a main concern at that time.[69, 70, 128, 130, 137]

To the best of my knowledge, the first publication of a stereotactic subthalamotomy of the region of the PSA was the one by Wertheimer et al. in 1960.[71] The interest in the procedure grew rapidly, however, after the meeting of the Harvey Cushing Society in 1963 where Andy presented the first series of subthalamotomies.[67, 68, 133] Several papers on the subject were published in rapid succession during the following few years, and although the subthalamotomy probably did not surpass the thalamotomy in usage, it apparently coexisted during the lesional era as an option for the treatment of movement disorders, especially when tremor was a dominating symptom.[134, 135, 137, 161, 167-170] The reports on subthalamotomy primarily concern PD and, secondly, ET, but conditions such as multiple sclerosis (MS) tremor, posttraumatic tremor, torticollis (cervical dystonia), cerebral palsy, and other movement disorders were also evaluated.[22, 66, 68-70, 125, 128, 130, 134-137, 140, 153, 161-163, 166-168, 170-186] In PD, the effects were reported as being most favorable on tremor and perhaps also rigidity, but the effects on bradykinesia and other symptoms are more difficult to interpret.[22, 66, 68-70, 125, 128, 130, 134, 135, 137, 140, 153, 161-163, 168, 170, 177-180, 187, 188]

Many groups, for example, the one working with Laitinen, combined lesions of the thalamus and the subthalamus according to the best response to intraoperative stimulation. Furthermore, several surgeons probably intentionally, as well as unintentionally, made both thalamic and subthalamic lesions and "labeled" them thalamotomy.[19, 22, 66, 125, 134, 135, 137-140, 166, 167, 171, 175, 176, 182, 185, 187, 189-194] However, the targeting and the studies concerning this issue were more detailed than one perhaps might think. The group of Bertrand and Velasco elaborated a method of minimizing the impact of the anatomical variations when using air ventriculography as the radiographic method. By dividing the ICL into tenths, they identified a quite small subthalamic "optimum" target area in which an alleviation of tremor could be reproduced in most patients. This area was located 8/10 behind the anterior commissure, 5/10 lateral to the midline and 1/10 to 2/10 inferior to the ICL. With a distance between the AC and the posterior commissure (PC) of 25 mm, i.e. the ICL length, the corresponding

coordinates would be 20 mm behind the AC, 12.5 mm lateral and 2.5–5.0 mm inferior to the ICL. The authors were quite specific that this area should be characterized as a "funnel", which thereby allowed greater variations in the inferior-superior (z) axis than in the anterior-posterior(y) or the lateral(x) axes. According to their data, this area corresponded to the Raprl, or, as stated in Velasco et al. in 1972, "the prelemniscal radiations within the Zona incerta."[70, 126, 128, 130]

Complications of Subthalamotomy

"Sir Bedevere: *What makes you think she's a witch?*
Peasant: *Well, she turned me into a newt!*
Sir Bedevere: *A newt?*
Peasant: [*meekly after a long pause*] *... I got better.*
Crowd: [*shouts*] *Burn her anyway!*

- Search for the Holy Grail, Monty Python, 1974

Complications of subthalamotomies will be discussed in somewhat more detail since three of the six papers in this thesis evaluate different safety aspects of DBS in the PSA. It has also been suggested that lesional surgery in the PSA was abandoned in favor of thalamic lesions due to the associated side effects.[196, 197] Some authors compared their thalamic and subthalamic lesions regarding the effect, as well as the side effects, of these procedures. The opinions differ and, unfortunately, it is difficult to draw conclusions based on these reports as to whether one target was more preferable than the other.[153, 163, 177, 178, 187, 198, 199]

Although often reported as mild, different types of cerebellar signs such as dysmetria, disturbances of gait and balance, dysarthria, and hypotonia were perhaps the most frequently reported category of side effects.[70, 127, 136, 166, 168, 169, 179, 180, 182, 189, 199, 200] Yasui et al. investigated the frequency of cerebellar signs after thalamotomy and subthalamotomy and found the frequency to be somewhat higher for subthalamotomy, and especially considering the persistence of these side effects.[199] Hypotonia was reported by several authors, and in a paper by Blacker et al., hypotonia accompanied by a slight transient clumsiness of the treated limb was reported in all of the 15 patients.[136]

Neglect of the treated arm secondary to thalamotomy has been reported by several authors. Velasco et al. also encountered this after combinations of thalamotomies and subthalamotomies, but it is difficult to know if this should be ascribed to the subthalamic lesion or not.[127, 129, 153, 201, 202]

Ipsilateral deficits of the sympathetic nervous system, presenting primarily with hypohidrosis and Horner's syndrome, was reported to occur quite frequently by some authors.[177, 203-205]

Dysphasia of different types and severity has been reported with quite high occurrences in some series of thalamotomies. Mild dysphasia was also reported after subthalamotomies by Lücking and Laitinen, but as Laitinen combined thalamic and subthalamic lesions, it is difficult, just as in the case of neglect discussed above, to draw any conclusions as to whether this was caused by thalamic lesions, subthalamic lesions, or both.[2, 22, 140, 180, 184, 201, 206-214]

"It is a cursed evil to any man to become as absorbed in any subject as I am in mine."

- *Charles Darwin*

Deep brain stimulation of the posterior subthalamic area

The subthalamotomy declined hand in hand with the other stereotactic procedures for movement disorders as the use of L-dopa for PD spread.[3] While DBS has revolutionized the field of stereotactic neurosurgery during the modern era, the interest in applying DBS to the PSA seems to have been fairly absent. Simplified, bilateral STN DBS has become the first choice for advanced PD and thalamic Vim DBS is mainly used for non-Parkinsonian tremors or tremor-dominant PD. The rationale for evaluating STN DBS was the knowledge gained from animal models (MPTP monkeys) about the role of the STN in Parkinsonism. Regarding Vim DBS, it seems as if it mostly depended on knowledge obtained from intraoperative stimulation during thalamotomies.[7, 104, 105] Based on the knowledge from the lesional era, one might feel that it would have been natural to explore PSA DBS for the same conditions as the subthalamotomy was once used.[3]

This was, in fact, also done several years before the publication in 1987 presenting high-frequency stimulation of Vim by Benabid et al., which is regarded by many as the first paper on DBS for movement disorders.[7, 215, 216]

In 1977 Mundinger published the article, "*Neue stereotaktisch-funktionelle Behandlungsmethode des Torticollis spasmodicus mit Hirnstimulatoren*", in which he presented 7 patients with spasmodic torticollis who had been treated with "*Permanentimplantation eines Hirnstimulationssystems (Medtronic ®) in die extra-pyramidalmotorischen thalamischen Kerne (V.o.a/V.o.i) und die subthalamische Zona Incerta unter Einbezug der Bündel H1 und H2 (nach Forel)*." In other words, this is, to the best of my knowledge, the first publication on chronic DBS which included the PSA. The results were reported to be good and not accompanied by complications.[217]

In The Lancet in 1980, Brice and McLellan published an article on two patients with MS tremor who were treated with chronic DBS using a target that was located in the subthalamic area. The coordinates where 20 mm behind the AC and 10 mm lateral and 6–8 inferior to the ICL.[218]

O.J Andy, who had presented the first series of subthalamotomies in 1963, published a paper in 1983 on nine patients with tremor of different etiology who were treated with chronic stimulation of different thalamic and subthalamic structures. The paper included one patient with posttraumatic tremor, for which the stimulated structures included the Zi and the effect was reported as "excellent".[219]

One may merely speculate as to why the DBS technique was not to become widespread based on papers published before 1987 and the reason why the PSA became a "forgotten target" is probably multifactorial. [3, 215-217, 219] It would take until the year 2000 before we saw the first publication on PSA DBS during the "modern era" of DBS. This and the subsequent reports on the subject are summarized in Table 1.[3, 196]

PSA DBS has been applied for various conditions with tremor, similar to the use of subthalamotomies. Apart from the patients in papers IV–VI, the therapeutic effect in 114 patients has been presented in 14 papers since the year 2000.[126, 141, 159, 160, 165, 196, 197, 220-228] There are essentially only four groups that have published series with PSA DBS: Kitagawa and Murata in Japan, Velasco and co-workers in Mexico, Plaha and Gill in the UK, and Blomstedt et al. in Sweden.[126, 141, 159, 160, 165, 196, 197, 220-222, 224-226, 229, 230] The intended targets and the nomenclatures of the procedures differ somewhat. Velasco et al. refer to their target as the prelemniscal radiations (Raprl), precisely as during the lesional era, Plaha et al. target

the caudal Zona incerta (cZi), and Kitagawa et al. refer to the posterior subthalamic white matter/area, which incorporates both the cZi and the Raprl.[126, 141, 165, 196, 197, 221]

The prefix 'caudal' regarding the Zi was added by Plaha et al. in order to distinguish this part of the Zi from the more anterior and superior part that is often affected when performing STN DBS.[141, 231-233] Our group refers to the cZi as our target since it reflects our intended anatomical target and corresponds to an area with a clear anatomical reference (i.e. lying posteromedial to the posterior tail of the STN). However, it is very difficult to separate the cZi from the Raprl on MRI images and the extension of the PSA is quite limited, and accordingly stimulation in the area probably affects several substructures.[3, 160, 224] We have therefore also chosen to use the term posterior subthalamic area as a general term for the area.[3, 159, 160, 224, 234]

Parkinson´s Disease and Parkinsonian Tremor

Excluding the 14 patients with tremor-dominant PD in paper VI of this thesis, 54 patients have so far been presented in six papers and one book chapter regarding PSA DBS for PD.[126, 141, 165, 221, 225-227] The improvements after DBS on the "cardinal motor signs" of PD have been reported as 78–93% for tremor, 45–94% for rigidity and 46–75% for bradykinesia. In essence, only 18 patients in two papers have been operated on with bilateral DBS due to the motor symptoms of advanced PD.[141, 225] The other series primarily include patients with tremor-dominant disease.[126, 165, 221, 226] There is also one publication by Khan et al. in which the patients received bilateral cZi DBS as well as DBS of the pedunculo-pontine nucleus (Ppn). These patients had a rather different clinical picture which was dominated by "*PD with significant falling, freezing, or postural instability.*"[227]

Although it involved only 5 patients, the article by Carrillo-Ruiz et al. concerning bilateral Raprl DBS for advanced PD reported quite impressive improvements in the motor part (part III) of the Unified Parkinson Disease Rating Scale (UPDRS).[225] Please see table 1 for details.

The article by Plaha et al. from 2006 is interesting since the group first performed STN DBS. Due to a better effect, the target was then moved medially of the STN, corresponding to the area of the pallidofugal fibers (outflow fibers from the Gpi) and the more anterior and superior parts of the Zi (outside the PSA).[141, 235] After further exploration, they once again moved their target, this time to the caudal Zi. According to their results, the best effect was elicited when stimulating the cZi with ensuing improvements contralaterally of 76% for the total UPDRS III, 93% for tremor, 76% for rigidity, and 65% for bradykinesia. The corresponding figures for the STN group were 55% for UPDRS III, 61% for tremor, 50% for rigidity, and 59% for bradykinesia.[141]

Essential tremor

As mentioned above, the PSA is often reached just by advancing a few millimeters inferior to the ICL when using a standard trajectory aimed at placing the electrode in Vim. Regardless of whether it is intended or not, the most inferior contacts of many "Vim electrodes" will therefore actually be located in the PSA.[3, 159, 160, 236] Several studies on the most effective contact location for Vim DBS in essential tremor have also shown that the most effective or energy-efficient stimulation site was actually located inferior to the thalamus within the PSA.[236-241] Sandvik et al. also compared a group with Vim DBS to one with PSA DBS for ET and found that the absolute majority of the contacts that yielded an effective reduction of tremor were located in the cZi or Raprl.[241]

Forty-eight patients from six papers have thus far been reported on concerning PSA DBS for ET (Table 1)..[160, 196, 197, 220-222] Including the 18 patients in paper V, there are now 22

patients for which the long-term effects of PSA DBS for ET have been evaluated.[220, 224] The results seem promising, even when compared with Vim DBS, which is currently the standard choice for DBS in ET. For bilateral procedures the improvements on the total Essential Tremor Rating Scale (ETRS) were 74–80%.[220-222] Blomstedt et al. presented the one-year results of 21 unilaterally operated patients, which improved 60% for total ETRS, 95% for contralateral hand tremor and 87% for contralateral hand function.[160]

Other types of tremor

The modern literature (excl. Paper IV) of PSA DBS for other types of tremor than ET and PD comprises four patients with MS tremor, two with dystonic tremor (DT) and one case each of posttraumatic tremor (PTT), cerebellar tremor (CT), Holmes tremor (HT), and spinocerebellar ataxia type 2.[196, 221, 223, 228] The results are reported as good and though it is still in its cradle, it seems as if PSA DBS may be a feasible procedure for tremor of various etiologies.

DBS of the Posterior Subthalamic Area in the Treatment of Movement Disorders					
Author	**Patients/Disease**	**Follow-up (months)**	**Target (mm)**	**Side effects**	**Results (improvement)**
Kitagawa 2000	1 ET & 1 DT unilat	-----	See Murata 2003	None reported	"Abolition" of tremor
Hooper 2001	1 PTT unilat	44	6 post MCP, 12 lat & 4 inf ICL	Transient weakness in the treated arm	Sustained ML-effect, electrode removed
Velasco 2001	10 PD unilat *Predominantly unilat tremor & rigidity*	12	Expressed in tenths of the ICL: Lat. 5/10, 8/10 post AC, 1–2/10 below ICL.	1 deter. depression, 1 subopt result due to stim-ind side-efx	Result reported to be excellent concerning tremor and rigidity.
Murata 2003	8 ET unilat*	Mean 23 (8-42)	10 lat of ICL. 3-4 post STN on the axial slice with the greatest STN-diameter. Active contacts: 11 lat, 7.5 post MCP, 4 inf ICL.	Only stimulation-induced which did not affect the result	Contralateral tremor improved by 81 %.
Plaha 2004	4 ET bilat	12	Medial to the posterior dorsal third of the STN.	None reported	Total ETRS improved by 80%. FMS improved 75.2 %.
Kitagawa 2005	8 PD unilat *Predominantly unilat tremor*	24	Contacts with best effect: Lat 10.5, 5.5 post MCP, 3 inf ICL.	None reported	C-lat tremor 78%, rigidity 93 %, akinesia 66%.
Plaha 2006	14 PD, 13 bilat & 1 unilat. *Therapy-refractory PD*	6	Active contacts: Lat 14, 6 post MCP, 2 inf ICL.	None reported	C-lat tremor 93%, rigidity 76 %, bradykinesia 65%.
Freund 2007	1 SCA type 2 bilat	24	2 contacts in Vim, 2 in the PSA	None reported	Nearly completely cessation of tremor and torticollis
Carrillo-Ruiz 2007 *Book Chapter*	PD 15 unilat †† PD 5 bilat *(all in C-R 2008)*	12	See Velasco 2001	None reported. See also C-R 2008	Not separated for bilat & unilat. See Velasco 2001 for unilat & C-R 2008 for bilat
Carrillo- Ruiz 2008	5 PD bilat ¤ *Advanced PD*	12	See Velasco 2001. Active contacts: Lat 11.5, 6.5 post MCP, 4.5 inf ICL.	1 deter. depression, 5 transient somnolence,	Total UPDRS III 65%, tremor 90%, rigidity 94 %, bradykinesia 75%.
Plaha 2008	6 ET, 5 PD, 4 MS, 1 CT, 1 HT, 1DT – all bilat *Tremor-dominant PD*	12	Posterior-medial to the posterior-dorsal STN.	1 transient dysphagia	PD: tremor 92 %, rigidity 77 %, bradykinesia 62 %. TRS: ET 76 %, MS 57 %, CT 60 %, HT 70 %, DT 71
Blomstedt 2009 *Paper IV*	2 DT, 1WT, 1CT, 1 NT	12	Posterior-medial to the STN at the level of the maximal diameter of the red nucleus.	1 hardware-related	Tremor & hand function DT 100%, WT 80% (incl. writing), CT 100%, NT 72%.Sust. ML-effect, electr. expl in 1 DT
Blomstedt 2010	19 ET unilat, 2 ET bilat	12	See Blomstedt 2009. Active contacts (mm): 11.6 lat, 6.3 post MCP, 3.0 inf of ICL.	8 trans dysphasia & 1 clumsiness. 1 subopt effect due to stim-ind side-efx. 3 hardware-rel.	ETRS improved 60%. Upper extr. tremor (item5/6) 95%. Hand function (item11-14) 87%.
Plaha 2011	15 ET bilat†	Mean 32 (12-84)	Posterior-medial to the posterior-dorsal STN	3 stim.-related dysarthria. 1 infection	ETRS improved 74%, FMS 73.5%
Khan, 2011 *Combined cZi & PPn DBS*	7 PD bilat *with significant falling, freezing, or postural instability*	12	Coordinates not stated. Posterior-medial to the posterior-dorsal STN	None reported to be related with the cZi	Tremor 84.6%, rigidity 45%, bradykinesia 46%
Fytagoridis 2011 *Paper V*	16 ET unilat, 2 ET bilat ±	Mean 48.5 (34-62)	See Blomstedt 2010. Active contacts (mm): 12.0 lat, 6.3 post MCP, 2.2 inf to ICL.	1 hardware-related	ETRS 52%. Tremor (item 5/6) 92%. Hand function 78%.
Blomstedt, 2012 *Paper VI*	14 PD, 13 unilat & 1 bilat *Tremor-dominant PD*		See Blomstedt 2009. Active contacts: Lat 12.6, 7.0 post MCP, 2.0 inf ICL	1 subopt result due to stim-ind side-efx. 1 infection	C-lat tremor 82.2%, rigidity 34.3%, bradykinesia 26.7%.

Table 1) Overview of the literature concerning PSA DBS for movement disorders. The figures in the column to the right represents improvement in percent with stimulation.
AC: Anterior commissure. MCP: Mid-commissural point. ICL: Intercommissural line. C-lat: contralateral. Inf: inferior. Post: posterior. Lat: laterality
FMS (functional motor score) = category used by Plaha et al.: upper limb action and postural tremor combined with items 10–14 (hand function & writing) of the ETRS.
*, One patient was previously presented in Kitagawa 2000. ††, 10 of 15 patients previously reported in Velasco 2001. ¤, All 5 patients were previously reported in Carrillo-Ruiz 2007. †, 6 patients were previously reported in Plaha 2008. ±, Long-term follow up of the patients from Blomstedt et al. 2010.
ET = Essential tremor; MS = multiple sclerosis; CT = cerebellar tremor; HT = Holmes tremor; DT = dystonic tremor; PTT = posttraumatic tremor. SCA 2= Spinocerebellar ataxia type 2. TRS = Fahn–Tolosa–Marin tremor rating scale

Zona incerta

"The region of which nothing certain can be said."- *Auguste Forel*

In 1877 Auguste Forel was the first to describe the Zi, "the zone of uncertainty". [242, 243] The Zi is a heterogeneous nucleus of the diencephalon that lies inferior to the ventrolateral thalamic nuclei and is draped over the superior and medial surfaces of the STN. Further inferiorly, the caudal extension of the Zi lies posteriomedial to the STN.[142, 143] The nucleus has been divided into four subsectors based on morphological and physiological properties and the caudal sector has been claimed to play a role in the motor system. [243-245] Even though some things have become less uncertain about the Zi, we still cannot fully comprehend its global role or if and how it plays a role in the pathophysiology of movement disorders.[141, 221, 243, 244] One thing that is known is that the Zi, with its different sectors, has extensive both afferent and efferent connections with virtually every part of the central nervous system. For example, there are reciprocal connections with the interpositus nuclei of the cerebellum, brain-stem motor nuclei, basal ganglia, thalamus, and cerebral cortex, but there seems to be limited direct connections with the STN.[245-252]

The transmitter substance of the efferent cZi axons is mainly γ-aminobutyric acid (GABA). GABA is inhibitory, in contrast to glutamate (Glu), which has an excitatory effect on the receiving neurons.[243, 253, 254]
In accord with the widespread connections to the Zi, experiments on rats have shown that Zi lesions can produce a variety of effects on, for example, arousal, attention, and motor and vegetative behavior. With regard to the motor system, the cZi seems be in a key position within the pathways connecting the cerebellum-thalamus-cortex and the basal ganglia-thalamus-cortex and also for modifying these projections via ascending sensory input.[243] The Zi has been shown to respond rapidly to peripheral stimulation and the Zi neurons seem to fire in synchrony with cortical impulses during normal movement.[248, 249, 255, 256] The quite extensive GABA-ergic and inhibitory axons that project from the Zi to the thalamus have been shown to block the sensory impulses to the thalamus and thereby reduce the spontaneous activity of the thalamic neurons.[255, 257, 258] In parkinsonian rats the Zi is hyperactive in similarity, but less marked in comparison, to the STN. It has been postulated that the predominately GABA-ergic Zi and the glutamatergic STN have parallel functions in the control of movements.[259, 260]

Prelemniscal Radiations

Currently, the most widely used stereotactic atlas for targeting deep brain structures is that of Schaltenbrand and Wahren. This atlas uses the nomenclature of Hassler which incorporates the preleminscal radiations and the fields H of Forel.[142, 143, 261] The Raprl signifies the fiber bundle anterior to the medial lemniscus (ml) and medial to the Zi (please see Figure 2).The Atlas of Morel was used in several studies in this thesis and this atlas has, instead, adapted the nomenclature used in studies of other primates. The intention of the Morel atlas was partly to provide an updated and detailed atlas, but also to simplify the transition of knowledge from studies in non-human primates to stereotactic neurosurgery in humans by using the same nomenclature. According to this nomenclature, the Raprl is incorporated into the cerebellothalamic tracts or the "fasciculus cerebellothalamicus (fct)", which also includes the "prerubral area", often referred to as the field H of Forel.[142, 261] The fct originates in the dentatus, interpositus, and fastigius nuclei of the cerebellum, passes along the superior cerebellar peduncle, and crosses the midline before it continues in between the Zi and the red nucleus and ascends into the thalamus.[261] Therefore, at the level of the PSA, the fct

corresponds more or less to the Raprl and it is very likely that what Hassler called Raprl mainly consists of cerebellothalamic fibers, but also axons from the mesencephalic reticular formation.[142, 164, 261]
Some neurophysiologic studies have been conducted during stereotactic operations on the Raprl. Stimulation of the median nerve of the forearm produced late, but not early, components of the somatosensory evoked potential (SEP) when recorded in the Raprl. These responses showed amplitude changes with attention, a pattern that is different from that of the medial lemniscus and the thalamus.[164, 262] Additionally, stimulation of the Raprl induced EEG-recruiting responses of the cortex similar to stimulation of the mesencephalic tegmental area.[164] These data favor the assumption that the fibers of the Raprl may have a role in the control of movements in relation to attention.

The Ventrolateral Thalamus

The nomenclature of the thalamic motor nuclei can be equally confusing as the one for the subthalamic structures. Most neurosurgeons are familiar with the Ventro intermediate nucleus (Vim) of thalamus according to the Schaltenbrand atlas and the nomenclature of Hassler. Later research have tried to cohere Hassler`s nomenclature with that used in other primates and have instead proposed the use of the terms ventral lateral nucleus of thalamus (VL) or Nucleus ventralis lateralis posterior thalami (VLp). The VL and VLp both incorporate the Vim, but they differ regarding whether other adjacent nuclei of Hassler such as Vop and/or Voi also should be included into each respective term or not.[142, 143, 263, 264]

Tremor

The aim with PSA DBS in movement disorders is not only to treat tremor. This section will, however, focus on tremor because this is the most important denominator for all the disorders included in this work.

Tremor is defined as a rhythmical and involuntary oscillatory movement of a body part. The tremor must be involuntary but the amplitude may vary. Rest tremor, which is predominately seen in PD, occurs in a body part that is not voluntarily activated and is completely supported against gravity. Action tremor is any tremor that is elicited by a voluntary contraction of a muscle. This category therefore includes postural, isometric, and kinetic tremor. Kinetic tremor is produced during any voluntary movement and is further divided into simple kinetic tremor (during movements that are not target-directed), tremor during target-directed movements (intention tremor), and task-specific tremors (for example, writing tremor).[265] The frequency of the oscillations in essential tremor normally varies between 4 and 12 Hz, while the rest tremor in PD has lower frequencies of 4–9 Hz.[265, 266]

The central neurogenic tremors such as for example essential, dystonic, cerebellar, and PD tremor are thought to arise from oscillations in the neural pathways of the brain. Data indicate that these oscillations are caused by not one, but multiple “oscillators” inside the respective loop. [266-268] Rest tremor is considered to arise from the basal ganglia loop and is, in most cases, dependant on dopamine depletion.[265, 266, 269] The action tremors are considered to arise somewhere in the neural loop connecting the inferior olive, cerebellar cortex, ventrolateral thalamus, and the motor cortex.[266] Studies have indicated that the ipsilateral cerebellum and the contralateral sensor-motor cortex and the thalamus are involved in ET, PD, and several other forms of tremor.[266, 269-271] The cerebello-thalamic pathways do, therefore, appear to be involved in the pathology of all tremors, even though the exact mechanisms and the roles of the different structures are unknown.

Why Deep Brain Stimulation of the Posterior Subthalamic Area for Movement Disorders?

"I know nothing expect the fact of my ignorance."

- Socrates

The mechanism of action for high frequency stimulation (HFS) of deep brain targets is at present under some debate. The exact mechanism of HFS in general and for the different targets in particular is not fully understood.[85, 272-276 277] The original theory was that HFS inhibited its targets since the effect of HFS mimicked lesions, but later data have indicated that this perhaps is not the only mechanism.[85, 276, 277]

To the best of my knowledge, there are two main theories concerning the putative effectiveness of DBS in the PSA. We might call one of these theories the "bottle-neck theory", after Herzog and co-workers, and the other "the cZi theory", after Plaha and co-workers.[221, 240]

The essence of the "bottle -neck theory" is similar to the ideas that Bertrand and Velasco postulated during the 1970s.[70, 128, 130, 240] The axon-dense PSA is considered to be a key point for interrupting or modulating pathological tremor signals within the cerebello-thalamo-cortical loop as they ascend from the cerebellar nuclei towards the VL. Herzog et al referred to the area as a "bottle neck" of axons emanating to the Vim and speculated that stimulation of these axons is more potent in terms of affecting thalamic neurons than stimulation of the thalamus itself.[240] This assumption is also supported by data showing that HFS potentially affects more neurons when stimulating axons, in contrast to nuclei.[276]

What we here call the "cZi theory" postulates that the cZi is an effective target for the alleviation of all forms of tremor due to its "unique GABA-ergic connections" with the basal ganglia and cerebello-thalamo-cortical loops, as well as the motor nuclei of the brainstem such as the inferior olive (IO) and medial reticular formation (MRF).[221] Plaha et al. suggest that the cZi is the only link between the basal ganglia and the VL and that alteration of this circuit is therefore effective in suppressing Parkinsonian tremor.[141, 221]

Regarding the action tremors, Plaha et al. suggest that abnormal oscillations are transferred from the cerebellar interpositus nuclei to the VL and MRF. These oscillations are also transferred to the cZi, which in turn sends efferents to the IO, MRF, RN, and also return signals to the interpositus in order to moderate and amplify the oscillations. cZi DBS is then thought to be effective by overriding oscillations in the nuclei mentioned above. Plaha et al. further propose that since the cZi DBS may influence the MRF, it may thereby affect the proximal component of tremor in contrast to stimulation of the VL or the cerebellothalamic fibers, which is said to be effective mostly against the distal components of tremor.[221]

In my opinion, neither of these theories actually excludes the other, and we also know that stimulation probably affects several of these microanatomic substructures. Thus, it is difficult to discard either one of them.

Background to the Present Study

Safety, Paper I-III

The safety aspects must be regarded as fundamental for all surgical procedures that are carried out solely in order to reduce symptoms and thereby improve the quality of life of the patients. Complications associated with surgery in the PSA are of particular interest, not only because the safety aspects of PSA DBS is relatively unexplored, but also because it has been suggested that the PSA was abandoned as a target for lesions due to the associated side effects.[126, 141, 165, 196, 197, 220-223, 225, 228] In paper I the first 40 patients undergoing PSA DBS at our department, regardless of the indication, were analyzed concerning complications and side effects.

Stimulation-induced side effects are quite seldom a threat to the results of DBS, but, nevertheless, important decisions are sometimes made based on them and they can also give us useful anatomical and physiological information about a target.[278, 279] To further explore the PSA in terms of safety, it could therefore be useful to investigate the panorama and the anatomical distribution of stimulation-induced side effects, particularly as these might differ from other more explored targets in the proximity, such as the Vim and the STN. In paper II stimulation-induced side effects were evaluated in relation to the anatomical location in patients with ET and PSA DBS.

Some of the patients with ET in paper I experienced a mild and transient postoperative dysphasia. Similar findings have not been reported after PSA DBS, but it has been reported for other targets such as the STN and Vim.[115, 280-282] To further investigate and, if possible, also objectify the effect that PSA DBS may have on language functions, the pilot study in paper III was conducted concerning the effects of cZi DBS on verbal fluency in a group of patients with ET.

Effect, Papers IV–VI

Several neurosurgeons preferred to target the PSA instead of the ventrolateral thalamus when treating various forms of tremor during the lesional era of functional stereotactic neurosurgery.[3, 22, 66, 70, 126] VIM DBS is by the majority of neurosurgeons considered as the standard procedure for tremor-dominant movement disorders other than PD. The number of modern studies reporting PSA DBS is more limited. Nevertheless, promising results have been shown for different movement disorders with tremor as a dominating symptom, such as tremor-dominant PD, ET, and other forms of tremor.[124, 126, 141, 160, 165, 196, 197, 220-223, 225, 228, 283, 284] In paper IV the effect of cZi DBS is evaluated in five patients with less common types of tremor.

Essential tremor is the most common adult movement disorder and up to 50% of the patients with disabling tremor do not respond adequately to drug therapy.[284, 285] For these patients DBS is an alternative which, in most cases, will become a life-long commitment and this highlights the impetus to also evaluate the long-term effectiveness of the procedure.[124, 284] Only four patients with ET have been reported on concerning the long-term results of cZi DBS and paper IV investigates this issue for 18 patients operated upon with cZi DBS for ET.[220]

DBS is a treatment alternative for symptoms of Parkinson`s disease when pharmacological therapy alone does not provide sufficient relief, or is associated with disabling side effects.[97, 286] At present bilateral STN DBS is the treatment of choice, but not all PD patients are suitable for this procedure. In some patients, another target for bilateral DBS or a unilateral procedure, is preferable.[83] For tremor-dominant PD, the most common

alternative target to STN is the Vim nucleus of the thalamus.[7, 83] Recent data has highlighted the PSA as an alternative target for PD, mostly for tremor-dominant disease, but effeteness has also been reported for bradykinesia and rigidity.
The aim of Paper VI was to evaluate the effect of unilateral cZi DBS on tremor in a group of patients with predominantly unilateral tremor-dominant PD.

Aims

- To evaluate the safety aspects of deep brain stimulation in the posterior subthalamic area.
- To investigate the panorama and the anatomical distribution of stimulation-induced side effects in the posterior subthalamic area.
- To investigate the relationship between verbal fluency and deep brain stimulation in the posterior subthalamic area.
- To evaluate deep brain stimulation of the caudal zona incerta for tremors other than ET and Parkinsonian tremor.
- To evaluate the long-term effect, energy consumption and safety of deep brain stimulation of the caudal zona incerta for Essential tremor.
- To evaluate the caudal zona incerta as a target for deep brain stimulation in the treatment of tremor-dominant Parkinson`s disease.

Material and Methods

"The beginning is the most important part of the work"
- Plato

Diagnosis
All patients were diagnosed by a neurologist and referred to surgery after failure of pharmacological treatment. ET and the other movement disorders except PD were diagnosed according to the "*consensus statement of the Movement Disorder Society on Tremor".* PD was diagnosed according the *"United Kingdom Parkinson's Disease Society Brain Bank Criteria".*[265, 287]

Ethics
Informed consent was obtained according to the Declaration of Helsinki and the studies were approved by the Ethical Committee of the University Hospital of Umeå (approvals 04-123M & 08-009M).

Paper I
Forty consecutive patients (67.5% men) operated on with DBS in the PSA were analyzed concerning complications and side effects of the procedure and followed for a mean period of 34 ± 18.2 months (range, 3–59 months). No patient was lost to follow-up due to migration, death, or any other causes. Twenty-seven patients had essential tremor (ET), 8 PD, 2 dystonic tremor, 1 cerebellar tremor, 1 neuropathic tremor, and 1 writing tremor. The mean age at surgery was 62 ± 13.0 years (range, 25–79).

Paper II
Twenty-eight consecutive patients with ET who underwent implantation of, in total, 33 DBS leads in the PSA from 2004 to 2009 were analyzed regarding stimulation-induced side effects. Twenty-four of the electrodes were on the left side and 9 on the right. Nineteen (67.9%) of the patients were men and the mean age at implantation was 61.

Paper III
This prospective study included 17 consecutive patients (7 females) treated with cZi DBS for ET. The mean age at surgery was 66. Two patients had bilateral surgery. Three of the unilateral procedures were performed on the right side, which in one case was for a left-handed patient. All 12 patients undergoing unilateral left-sided procedures were right-handed.

Paper IV
Five patients with unilateral PSA DBS for tremor were included in this prospective study. Two patients had dystonic tremor, one primary writing tremor, one cerebellar tremor, and one neuropathic tremor. The group consisted of three men and two women. The mean age at surgery was 49.

Paper V
The one-year outcome for the 18 patients with ET in Paper V has been presented previously in a study on 21 patients.[160] Three of the patients from the original study did not, however, complete the long-term follow-up. One patient died of causes not related to the surgery and two patients did not wish to participate owing to old age, declining health, and long travelling distances. Twelve patients were males and six were females. The mean age at operation was

63 and the duration of disease 20.3 ± 13.9 years. Fourteen patients had left-sided, two right-sided, and two bilateral implants.

Paper VI
Fourteen consecutive patients (12 men) were included in this prospective study on unilateral cZi DBS for PD. The mean age at the time of surgery was 65 and the duration of disease 7 ± 5.7 years. Five patients had non-L-dopa responsive symptoms (≤ 30% improvement of the UPDRS III score on 1.5 times their normal L-dopa dose). The indication for DBS in all patients was disabling tremor with unilateral predominance and insufficient relief with pharmacologic therapy. In three patients the symptoms may have justified a bilateral procedure, but this was excluded due to a moderate cognitive decline.

Eleven patients were operated upon on the left side, two on the right, and one had bilateral staged surgery. The second procedure in the latter patient was performed after an interval of five years due to progression of symptoms and the patient's UPDRS scores were evaluated separately for each electrode.

Evaluation and Visualization

The stereotactic coordinates of all contacts were calculated from a postoperative stereotactic CT. The Framelink® planning station was then used to fuse the pre- and postoperative images and to calculate the coordinates for each contact in relation to the midcommissural point (MCP), and regarding paper II and VI also in relation to the posterior tip of the STN at the level of the maximal diameter of the red nucleus (pSTN). In papers II and V-VI all contacts were plotted on the stereotactic atlas of Morel and a 3D atlas was created based on the axial images of this atlas.[142] The software tool used for visualization was created in Matlab 7.0 (The MathWorks, Inc., USA).

In paper II, each contact of the implanted electrode was evaluated in a standardized fashion one year after surgery using monopolar stimulation, a pulse width of 60 μsec and a frequency of 145 Hz. The amplitude was gradually increased up to 4.5 V, or less if the patient experienced intolerable side effects. The side effects were recorded at the amplitude at which they first appeared and were categorized according to Table 3 in the Result section. Each side effect was visualized with a spherical 3D object in the 3D atlas (radius 0.3 mm) which was color-coded according to the type of side effect (Figures 6 and 7 in the Result section). In cases where multiple side effects were presented by the same contact, each side effect was represented by a separate sphere with an offset location of 0.3 mm.

The patients in paper III were evaluated regarding verbal fluency before surgery, three days after surgery and, finally, after one year. The early postoperative evaluation was performed before the stimulation had been initiated, and the late postoperative evaluation after the stimulation had been turned off during the night. The test consisted of four different subtests, for which one minute each was allotted. In the first test the patient was asked to mention as many words as possible beginning with the letter A; in the second test, five-letter words beginning with M; in the third, names of professions beginning with B; in the fourth, five-letter names of animals beginning with S. Finally, at the one-year follow-up, ten patients were also evaluated using the same test on-stimulation, in addition to the test made off-stimulation. This was a later addition to the study and was not done in the first patients.

In paper IV the patients were evaluated using items from the ETRS before surgery, and off/on-stimulation after one year.[288] The evaluation off-stimulation was performed after the DBS had been deactivated during the night. The items used were item 5/6 (resting, postural and action/intention tremor of the upper extremity), items 11–14 (hand function tested by drawing and pouring water), as well as item 10 (handwriting) if the patient wrote with the treated hand.

In paper V the patients were evaluated before and off/on-stimulation after one year, and at the final evaluation after three to five years using the ETRS.[288] The evaluation off-stimulation was performed after the DBS had been deactivated during the night. The two patients with bilateral stimulation were evaluated separately for each electrode.

The patients in paper VI were evaluated according to the UPDRS III (motor part) on/off medication before surgery and at a minimum of 12 months postoperatively on/off medication and stimulation. The off-medication evaluations were performed in the morning after the medication had been withheld for about 12 hours. The evaluations off- and on-stimulation were performed after the stimulator had been switched off/on, for 60 minutes.
The contacts used for chronic stimulation in paper II, V and VI are visualized in Figures 5, 13, and 15, respectively.

Surgical technique

The Leksell frame model G® (Elekta Instrument AB, Linköping, Sweden) was placed the day before surgery or during the morning of the procedure. Stereotactic MRI was performed after placement of the frame, and calculations of the target and trajectory were done using the Framelink Planning Station® (Medtronic, Minneapolis, MN, USA).

The target was identified anatomically on stereotactic T2-weighted transaxial MRI images as lying slightly posterior and medial to the visualized posterior tail of the STN on the scan showing the maximal diameter of the red nucleus (Figure 3). Intravenous cefuroxim was given as antibiotic prophylaxis. The procedures were performed under local anesthesia and intraoperative effects and side effects were evaluated using macrostimulation through the various contacts of the permanent DBS electrode 3387 or 3389 (Medtronic, Minneapolis, MN, USA). Microelectrode recording was not done. The electrode was secured with the Stimloc™ burr hole cover (Medtronic, Minneapolis, MN, USA) and the connection between the electrode and the extension cable was placed on the calvarium. In all but three cases the implantable pulse generator (IPG) was placed in the same session. A stereotactic CT scan for verification of the electrode position was performed before removing the Leksell frame.

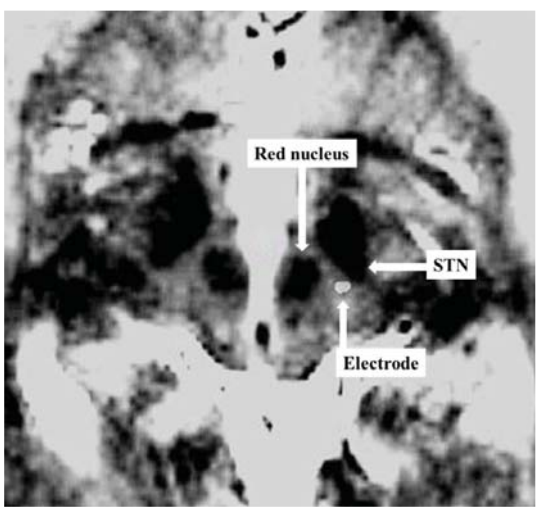


Figure 3) Preoperative T2-weighted MRI fused with a postoperative CT demonstrating the electrode in the left posterior subthalamic area. The image is at the level of the maximal diameter of the red nucleus.

Statistics

Results are presented as the mean, ± standard deviation (SD) and, in some cases, also the range. Paired t-tests were used to compare means of verbal fluency in paper III. The non-parametric Wilcoxon signed rank test was used for statistical comparison between pre-operative and post-operative scores, and between on and off stimulation in papers IV-VI.

ANOVA for repeated measurements with the Bonferroni test as a *post hoc* test was used for comparison between the stimulator settings in paper V. A p value of ≤ 0.05 was considered statistically significant.

Results

Paper I

Fifty-four DBS leads were implanted in these 40 patients, requiring a total of 57 tracks. Twenty-nine patients were operated on in the left hemisphere, 7 in the right and 4 bilaterally. Five of the patients had an ipsilateral lead implanted at a different target (4 STN, 1 Vim) due to participation in a separate study. Four patients received an extra ipsilateral electrode in the PSA due to an ambiguous response during intraoperative stimulation of the original electrode.

The deepest contacts (contact 0) were localized at a mean laterality of 10.9 ± 1.2 mm from the midline, 7.6 ± 1.5 mm behind the mid-commissural point, and 4.4 ± 1.9 mm below the inter-commissural line, while the corresponding figures for the chronically used contacts were 12.0 ± 1.3 mm, 6.1 ± 1.5 mm and 1.5 ± 1.9 mm, respectively. The patients were hospitalized for a mean of 7.4 ± 2.0 days.

Table 2) Side-effects encountered among 40 patients, with 42 procedures and 54 leads implanted

Side-effects	No
Transient dysphasia	9
Transient clumsiness	2
Transient hemiparesis with persisting dizziness	1
Rebound of tremor	2
Suboptimal effect on tremor due to stimulation induced side-effects	1
Hardware related complications other than infection	4
Infection	1
Seizure	1
Total number of side-effects	21

General Complications

The encountered complications in this series are summarized in Table 2. Two procedures were aborted in the operating room and completed at a later time: in one case because the durotomy provoked a generalized seizure and, in the second case, due to suboptimal placement of the electrode in a patient too exhausted to allow a relocation of the electrode in the same session.

No hemorrhages were seen in this series. A 72-year-old patient developed mild contralateral hemiparesis after the operation. No hemorrhage or other findings of interest were seen at repeated CT scans. The hemiparesis had regressed completely at the evaluation after 6 months, but the patient had developed possible sequelae in the form of dizziness when standing up, forcing her to use a walking support when walking outside of the home. The dizziness was not improved by turning off the stimulation.

During the period after discharge, two patients experienced transient clumsiness of the contralateral hand and leg and of the contralateral hand, respectively. These symptoms had resolved, however, before the evaluation at 6 weeks, and no objective findings were present at the examination.

Nine patients with ET developed mild postoperative dysphasia, which regressed completely within 1 day to 5 weeks. Among these patients, 7 had been operated on in the left hemisphere, 1 in the right (patient is right-handed) and 1 bilaterally. Five of these patients had received an extra ipsilateral electrode, 2 patients in the STN, 2 in the PSA, and 1 in the Vim.

Stimulation-induced side effects

The stimulation-induced side effects did normally not impede the final result. However, in one patient the electrode was placed too anterior and too medially close to the red nucleus (contact 0: laterality 7.6 mm, 5.3 mm behind the MCP, 4,3 below the ICL.) and an optimal result could not be reached without eliciting visual disturbances and dizziness. In this patient a suboptimal reduction of tremor was therefore accepted in order to avoid these side-effects.

A stimulation-induced and quite profuse ipsilateral hyperhidrosis of the back, chest and forehead was seen in a patient with a left-sided DBS for ET. This disappeared after adjustment of the stimulation parameters, and no concurrent symptoms were observed.

A disturbing transient rebound of tremor was encountered on turning off the stimulation in two patients with PD. This problem ceased after the stimulation had been modified.

Hardware-Related Complications

One patient with PD and bilateral implants suffered a postoperative infection. Three days after surgery he developed fever, elevated C-reactive protein, mild intermittent confusion, and a discrete left-sided hemiparesis. Signs of inflammation were seen along the right cerebral electrode (Figure 4). The electrode was removed and samples for bacteriological culture were collected. The cultures were negative and the patient was treated presumptively with antibiotics and recovered fully within one month. However, after three months the scar over the left electrode became purulent. The second electrode was removed and cultures demonstrated growth of coagulase-negative Staphylococcus aureus, Enterobacter aerogenes and α-hemolytic Streptococcus. This patient did not suffer any permanent sequelae.

Revision of the extension cables was performed in two patients due to straining and a feeling of tightness and one patient had an irritating granuloma removed from the infraclavicular scar.

The IPG malfunctioned in one of the patients with two ipsilateral electrodes with regard to the STN electrode. This did not affect the clinical result, however.

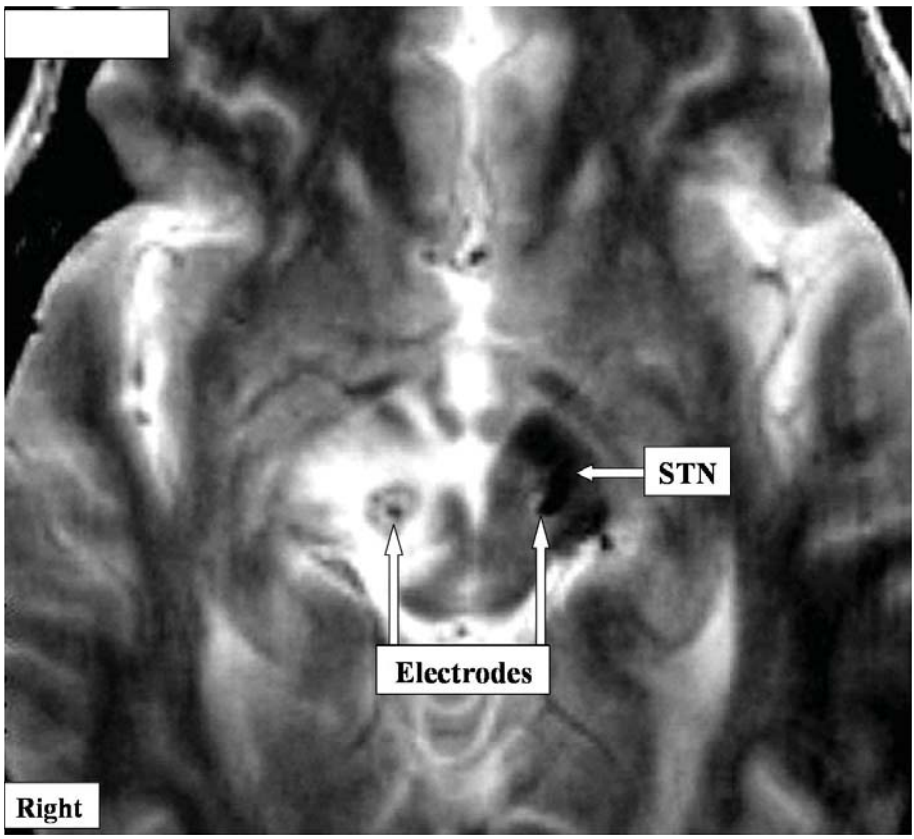


Figure 4) T2 weighted MRI showing oedema as a sign of inflammation along the right electrode. *(Reprinted with kind permission from the publishers.[159])*

Paper II

Thirty-three electrodes, in total 132 contacts, were evaluated and 331 stimulation-induced side effects were recorded, two thirds of which were paresthesias. Table 3 shows the overall frequency of the different types of side effects and the mean amplitudes and coordinates of the contacts giving rise to them. All contacts are visualized in Figure 5, and the contacts that caused side effects are visualized in Figure 6 for paresthesias and in Figure 7 for the remaining categories. Contacts causing dysarthria, ataxia/dysmetria, and muscular affection are visualized in a 3D model of the area outlined by the red nucleus and the STN (Figures 8a and 8b). This model was made using the pSTN as the origin for Figure 8a, and the MCP as the origin for Figure 8b.

Side-effect	No	X	Y	Z	Amplitude (V)
1.Paresthesias	219				
Hand	75	**11,7** ±1,5 (8,6 – 15,4)	**-6,3** ±1.6 (-9,8– -1,7)	**-2,3** ±2,7 (-7,1 – 3,8)	**1,7** ±0,9 (0,3 – 4)
Face	71	**11,6** ±1,6 (8,4 – 16,0)	**-6,3** ±1,9 (-1,2 – -10,2)	**-2,5** ±2,6 (-7,6 – 4,0)	**2,2** ±1,0 (0,8 – 4,5)
Arm	32	**11,2** ±1,4 (8,4 – 14,5)	**-6,4** ±1,8 (-9,4 – -1,8)	**-3,1** (±2,2) (-6,0 – 1,4)	**2,0** ±0,8 0,3 – 3,6
Leg	39	**11,8** ±1,3 (9,2 – 15,0)	**-6,5** ±1,6 (-2,4 – -8,8)	**-3,6**± 2,5 (-7,9 – 3,4)	**2,1** ±1,1 (0,6 – 4,5)
2. Dizziness	32	**11,8** ±1,5 (9,5 – 15,4)	**-6,0** ±1,5 (-9,1 – -1,7)	**-2,4** ±2,6 -7,9 – 3,8	**3,2** ±0,8 (1,3 – 4,5)
3. Blurred vision	26	**11,8** ±1,8 (8,4 – 15,0)	**-5,7** ±1,7 (-8,8 – -2,3)	**-1,3** ±2,8 (-6,3 – 4,0)	**3,2** ±0,7 (1,5 – 4,2)
4.Muscular affection	19	**12,7** ±1,7 (10,3– 16,0)	**-6,0** ±1,8 (-9,8 – -2,4)	**-2,6** ±2,6 (-7,9 – 2,0)	**2,9** ±0,8 (1,5 – 4,5)
5. Dysarthria	15	**12,4** ±2.1 (9.3 – 16.0)	**-5,2** ±1,5 (-7,1 – -1,9)	**-0,9** ±2,6 (-5,2 – 3,4)	**3,2** ±0,6 (1,8 – 4,1)
6.Ataxia/dysmetria	13	**11,3** ±1,2 9,2 – 13,2	**-5,4** ±1,8 (-7,2 – -1,7)	**- 2,4** ±3.0 (-6,8 – 3,8)	**3,0** ±0,9 (2 – 4,5)
7. Diplopia	4	**9,4** ±1,3 (8,4 – 11,3)	**-5,1** ±2,6 (-7,2 – -1,8)	**-3,7** ±2,2 (-1.5 – -6,3)	**3,3** ±0,2 (3 – 3,6)
8.Ptosis	2	**12,5** (12.1 – 12,9)	**-6,8** (-5 – -8,5)	**-2.0** (-0,7 – -3,2)	**3,6** (3,3 – 3,9)
9.Hyperhidrosis	1	**11,6**	**-6,1**	**-4,4**	**3,0**
Total	**331**				

Table 3) Categorization and frequency of appearance of the encountered stimulation induced side-effects. The mean coordinates in the three stereotactic axis's are given. Values are mean (SD±) (range).

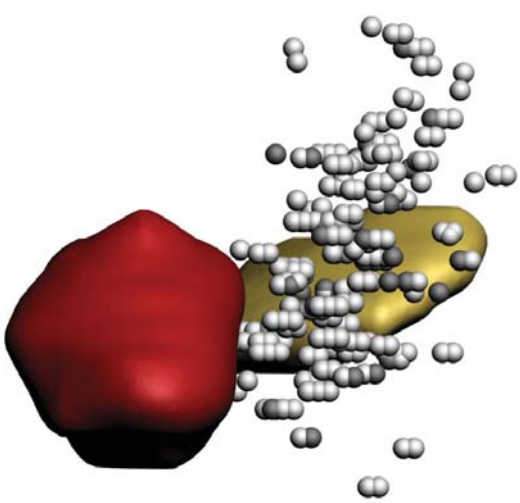


Figure 5) A 3 D reconstruction (posterior view) depicting all implanted contacts in Paper II, except those not visible in this view due to screening. The contacts are shown in relation to the red nucleus (red) and STN (golden), the reconstruction was made based on the MCP as origin. Contacts used for chronic stimulation are dark

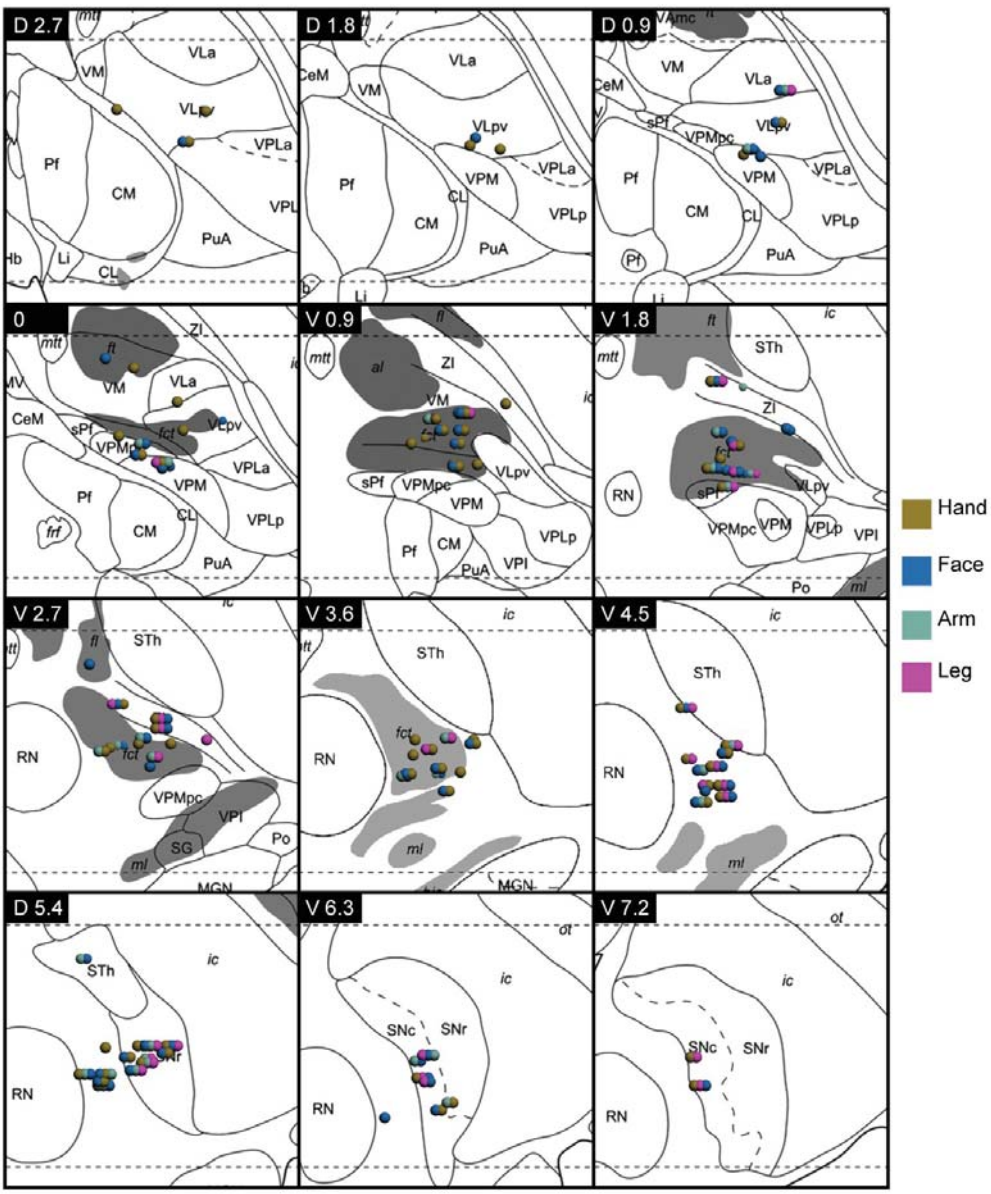


Figure 6) Contacts eliciting stimulation-induced paresthesias plotted on axial slides of the Morel Atlas. Slide 0 represents the AC-PC plane and the images are separated by 0.9 mm. Dorsal (D) or Ventral (V) to the midcommissural point.

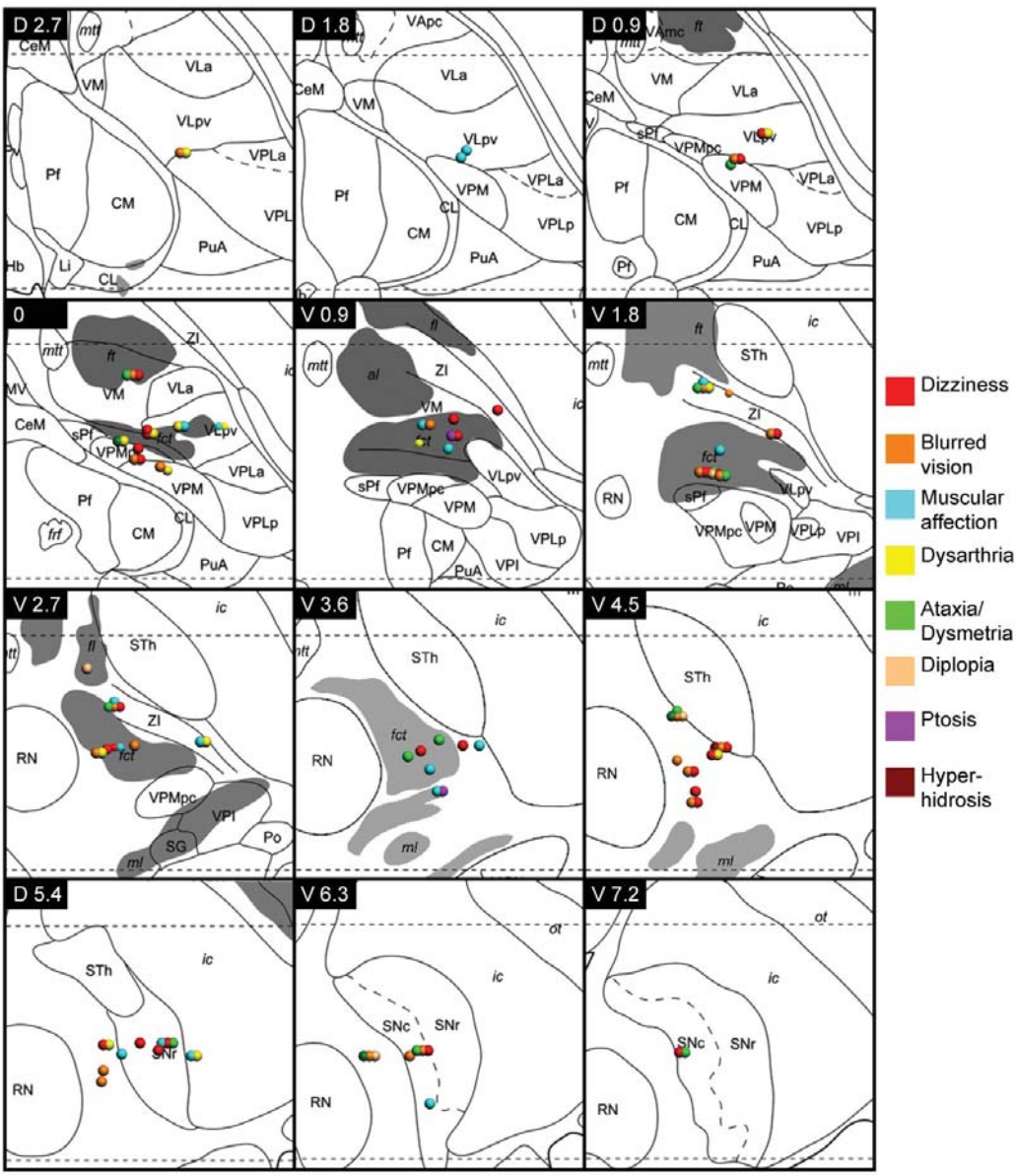


Figure 7) Contacts eliciting different stimulation-induced side effects are plotted on axial slides of the Morel Atlas. Slide 0 represents the AC-PC plane and the images are separated by 0.9 mm. Dorsal (D) or Ventral (V) to the midcommissural point.

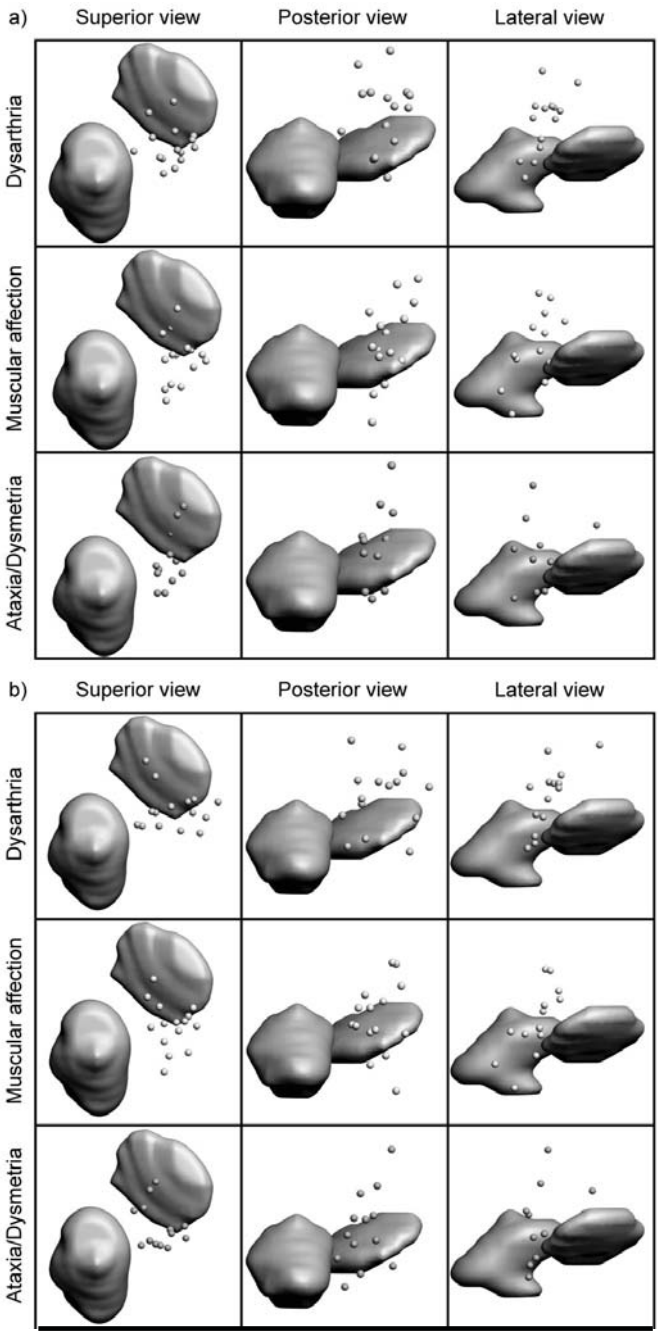


Figure 8a and Figure 8b) 3D reconstruction of the area outlined medially by the red nucleus (RN) and anterolaterally by the STN depicting contacts where stimulation caused dysarthria, muscular affection, or ataxia/dysmetria. The posterior tip of STN at the level of the maximal diameter of the RN (pSTN) was used as origin in 8a instead of the conventionally used midcommissural point, which was used in 8b for comparison.

Paper III

Verbal Fluency Before versus After Surgery

The results regarding verbal fluency are presented in Figures 9 and 10. The total score decreased from 22.7 ± 10.9 before surgery to 18.1 ± 7.5 immediately after surgery (t (16) = 2.2898, $p = 0.0360$). The mean total score one year after surgery with the stimulation turned off was 20.1 ± 9.7 (n.s., t (16) =1.1481, $p = 0.2678$). The data from the last subtest were excluded in an additional analysis in order to rule out possible floor effects, however, without significantly changing the results. In the ten patients evaluated on- and off-stimulation the mean total scores were 24.0 ± 8.0 and 24.1 ± 8.5, respectively (n.s.)

No side effects thought to be able to affect the outcome of the tests of verbal fluency were seen, with the exception of a mild and transient dysphasia reported by four patients. These patients did not, however, have a larger reduction of verbal fluency than those patients who did not report postoperative dysphasia.

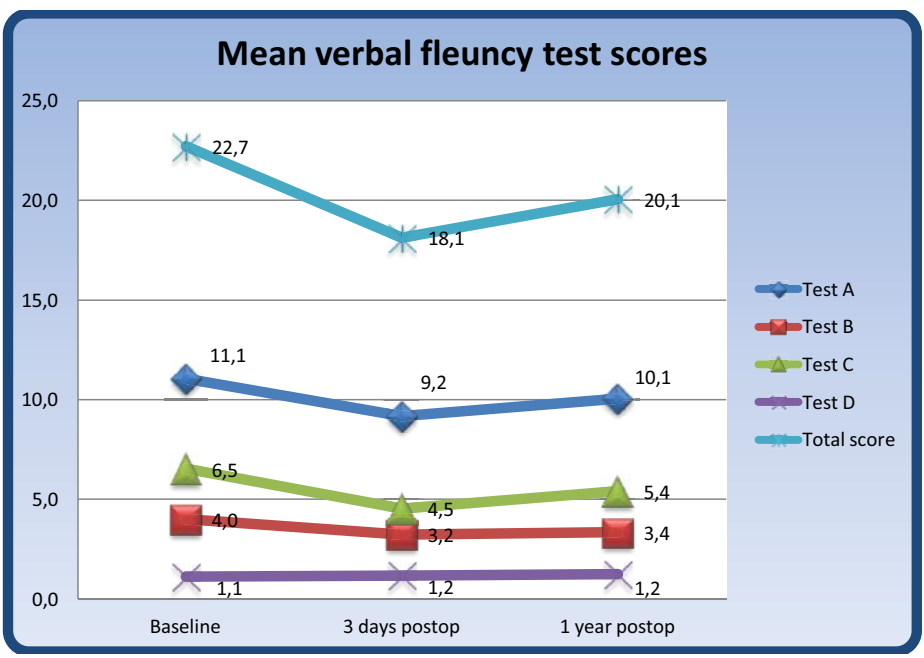
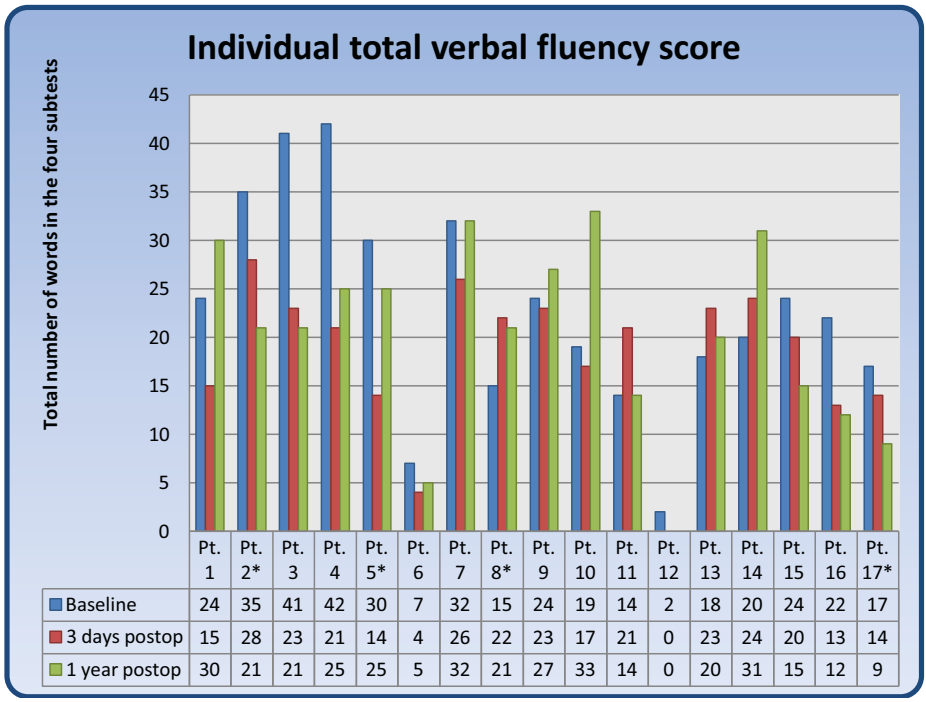


Figure 9) Mean scores for the group on tests A to D and the total score of the verbal fluency tests before surgery, three days after surgery and one year after surgery.
A = As many words as possible beginning with the letter A
B = Five-letter words beginning with M
C = Names of profession beginning with B
D = Five-letter names of animals beginning with S



	Pt. 1	Pt. 2*	Pt. 3	Pt. 4	Pt. 5*	Pt. 6	Pt. 7	Pt. 8*	Pt. 9	Pt. 10	Pt. 11	Pt. 12	Pt. 13	Pt. 14	Pt. 15	Pt. 16	Pt. 17*
Baseline	24	35	41	42	30	7	32	15	24	19	14	2	18	20	24	22	17
3 days postop	15	28	23	21	14	4	26	22	23	17	21	0	23	24	20	13	14
1 year postop	30	21	21	25	25	5	32	21	27	33	14	0	20	31	15	12	9

Figure 10) Individual total scores (including subtests A to D) at each evaluation are illustrated with bars as well as with numbers. * Patients who experienced transient subjective dysphasia.

Paper IV

Results and Case Presentation
At the follow-up after one year, the mean score on the tested items of the contralateral hand had improved from 17.2 ± 12 points preoperatively to 7.6 ± 10.6 "off-stimulation" and 2.2 ± 4.4 "on-stimulation". Only the reduction between baseline and "on stimulation" was statistically significant. The results are also further presented in Figure 11. No major complication occurred. Due to the limited size of this series, each patient will be presented in brief below.

Patient 1 - dystonic tremor
This left-handed female had a quite sudden onset with symptoms of clumsiness, ache, tension, and tremor in the left arm at the age of 30. MRI of the brain was normal. Some dystonic posturing was seen in the left arm and the tremor of the left hand was distal and of rather high frequency. She had a mild intermittent resting tremor, a moderate postural tremor, and a moderate tremor of action. She was diagnosed as having a dystonic tremor.

Pharmacological treatment did not improve the patient and at the age of 38 she underwent DBS of the right PSA. She experienced a pronounced microlesional effect and was initially completely free of tremor for several weeks. Regarding tremor and hand function of the left arm, the patient improved from 9 points before surgery to 3 "off-stimulation", and 0 "on-stimulation" one year after surgery. No dystonic posturing was seen and the ache and tension had disappeared completely.
The best effect was achieved on contact 0 (9.5 mm lateral to the midline, 4.5 mm behind MCP, 3.5 mm below ICL) and the patient used monopolar stimulation with 2.1 V, 60 µs, and 185 Hz.

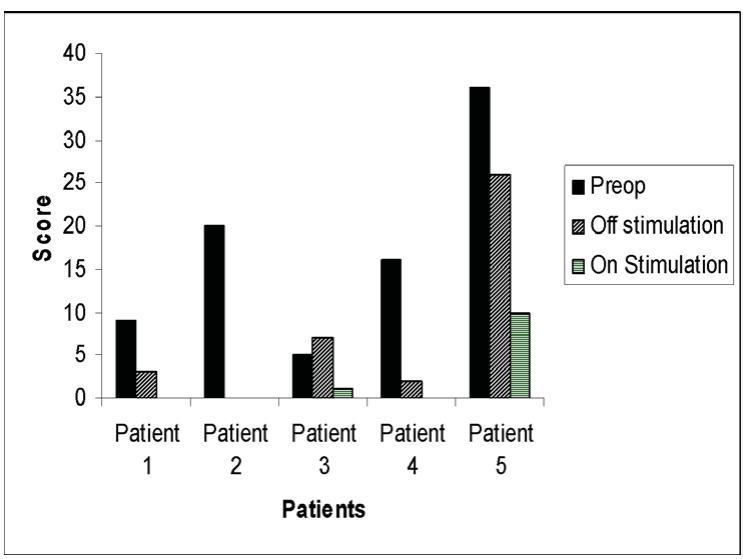


Figure 11) This demonstrates the scores for item 5/6 (tremor), item 10 (handwriting) when appropriate, and items 11-14 (handfunction) preoperatively and 'off-' and 'on stimulation' one year after surgery in patient 1-5. *(Reprinted with kind permission from the publishers.[159])*

Patient 2 - dystonic tremor

The symptoms of this left-handed male started with chronic pain in the neck and left arm after a traffic accident with whiplash trauma at the age of 29. Many years later intermittent dystonic phenomena and a clinically insignificant intermittent tremor in the left hand were noted.

At the age of 40 the patient developed pain, a feeling of tension, and tremor in the right arm. He had a mostly distal tremor of high frequency that was present at rest, when maintaining posture, and during activity. The tremor was always present, except for when the patient rotated his head toward the right side and at the same time tilted his head to the right side (*geste antagoniste*) when it disappeared completely. The condition was diagnosed as a dystonic tremor.

He was operated on at the age of 45 with left-sided PSA DBS (Figure 12). The deepest contact was placed 10 mm lateral to the midline, 7 mm behind MCP, and 5 mm below ICL. He had a pronounced and sustained microlesional effect and has been completely free of tremor ever since. The IPG was therefore later explanted.

Patient 3 - writing tremor

In this right-handed female the symptoms started at the age of 56, with tremor while writing. This gradually increased in strength and eventually her ability to use a computer 'mouse' was also affected. No tremor was noted when performing other tasks, but the condition was highly incapacitating for the patient in her daily work. She was diagnosed with a primary writing tremor type B (position specific).

She was operated on at the age of 64 with left PSA DBS. Before surgery she scored 5 points when evaluated for writing and function of the right hand (items 10–13). One year after surgery she scored 7 points off-stimulation and 1 on-stimulation. Her writing velocity further improved substantially and she considered herself to have no remaining disability when writing or working the computer mouse on-stimulation. At the follow-up she had bipolar stimulation using 2.8 V, 60 μs, and 185 Hz with contact 0 negative (11.5 mm lateral to the midline, 6 mm behind MCP, 3.5 mm below ICL) and contact 1 positive.

Patient 4 - cerebellar tremor

This patient was operated on at the age of 14 for a juvenile astrocytoma that occupied the major part of the right cerebellar hemisphere. No recurrence of the tumor has occurred. At follow-up after surgery, tremor and affection of the fine motor skills in the right upper extremity were present. The tremor progressed with time, and the patient was operated on at the age of 24 with DBS of the left Vim. The result was marked reduction of the tremor, although the patient never became completely free of tremor. The tremor continued to progress after surgery with development of a more pronounced proximal component, which could not be controlled by DBS. At examination the patient demonstrated a cerebellar tremor of low frequency and mixed low and high amplitude with frequent large jerky movements from the shoulder/upper arm. It was a postural- and action/intention tremor without any tremor at rest.

At age 34 the electrode broke and it was decided to replace it with a new one in the PSA. Macrostimulation during surgery did not yield an optimal effect, and it was decided to implant a second electrode in the same location as the broken electrode in the Vim. Nor did this electrode produce a good response. However, an excellent effect could be achieved with the PSA electrode after the stimulation-parameters were optimized postoperatively. Even if there was no microlesional effect immediate after surgery, there was an apparent effect even without stimulation after one year. As for tremor and hand function, the patient improved from16 points before surgery to 2 points off-stimulation and 0 points on-stimulation. The

patient has managed without stimulation in everyday life without problems, but often used the DBS since he felt that it improved the motor skills of the hand and that it abolished occasional jerky twists in the shoulder.

At follow-up the patient had 6.3V, 90 μS, and 145 Hz bipolar stimulation with contact 1 (10 mm lateral to the midline, 8 mm behind MCP, 3.5 mm below ICL) and 2 negative and 3 positive.

Patient 5 – neuropathic tremor

This right-handed man had a history of previous abuse of alcohol and amphetamine. At the age of 30 diabetes started and over the years he developed retinopathy, arteriosclerosis, orthostatism, impaired balance and gait, and a severe peripheral neuropathy. Tremor started in the right arm at the age of 64 and spread to affect the other extremities as well as the head. In the arms, it was a high amplitude rest-, postural- and especially intention/action tremor. DaT scan and MRI were normal and the condition was diagnosed as neuropathic tremor. The patient underwent left PSA DBS at the age of 66. During the first months, he showed an excellent effect of stimulation and was virtually free of tremor in the right arm.

As for tremor of action/intention, the effect was excellent for the distal component. The effect on the proximal component did diminish, however, somewhat after six months and even more after one year. The patient scored 36 points for tremor and hand function of the right arm before surgery and after one year this was reduced to 26 off-stimulation and 10 on-stimulation. The stimulation did also abolish the head tremor. At follow-up the patient had 3 V, 60 μS, and185 Hz bipolar stimulation with contact 1 (10.5 mm lateral to the midline, 7 mm behind MCP, 2 mm below ICL) and 2 negative, 3 positive.

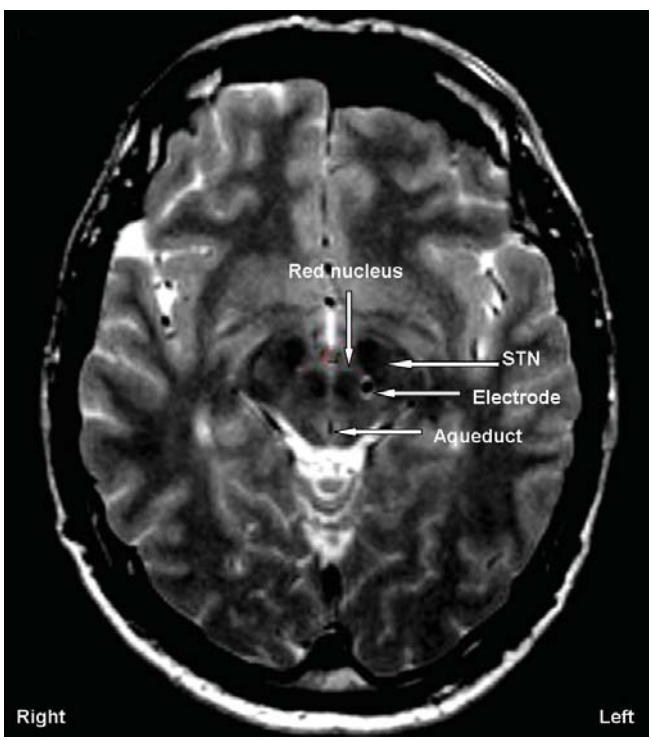


Figure 12) Postoperative MRI demonstrating the electrode in the left posterior subthalamic area in patient 2. *(Reprinted with kind permission from the publishers.[159])*

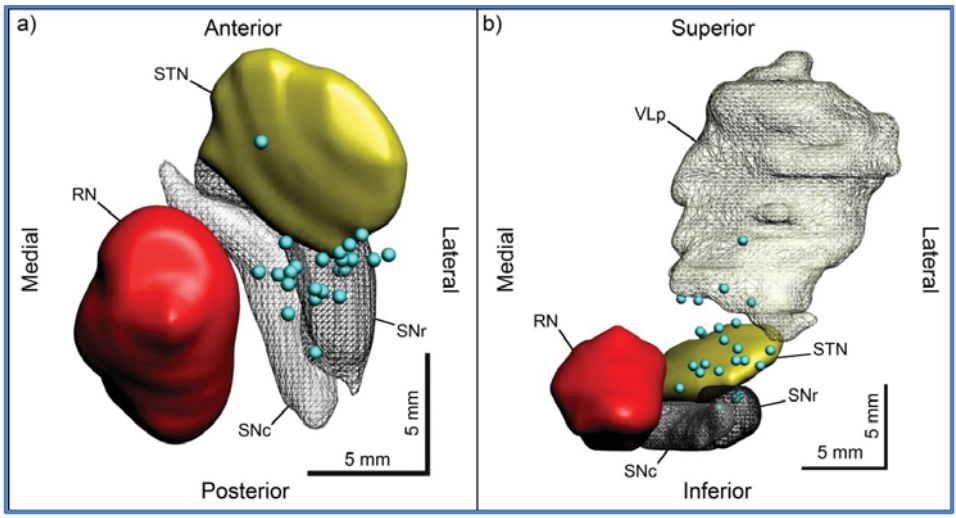


Figure 13a and b) Illustration demonstrating the location of all contacts in the PSA used for chronic stimulation in Paper V and adjacent structures that outline the area. **a)** Superior view. **b)** Posterior view. Both illustrations were made by plotting the contacts on the axial images of the stereotactic atlas of Morel and a 3D atlas was created by using the Matlab 7.0 (The MathWorks, Inc., USA) software. *(Reprinted with kind permission from the publishers.[224])*
STN - Nucleus subthalamicus. RN - Nucleus ruber. VLp - Nucleus ventralis lateralis posterior thalami. SNc - Substantia nigra pars compacta. SNr - Substantia nigra pars reticulata.

Paper V

Eighteen patients with 20 DBS electrodes were evaluated at the final evaluation after three to five years, mean 48.5 ± 10.6 (range 34–62) months after surgery. The contacts used for chronic stimulation were located 12.0 ± 1.5 mm lateral to the midline, 6.3 ± 1.5 mm posterior to the midcommissural point and 2.2 ± 2.3 mm inferior to the intercommissural line. The contacts used for chronic stimulation are illustrated in Figure 13, a 3D model based on the axial slides of the stereotactic atlas of Morel that displays the target area and the anatomical structures in the vicinity of the PSA.[142]

Tremor assessment
The total ETRS score and selected subscores are presented in Table 4 and Figure 14. The percentage improvement on-stimulation at both postoperative evaluations is compared in Table 5.

On-stimulation the total ETRS score was 17.6 ± 8.2 after one year and 21.9 ± 10.0 at the final evaluation, representing improvements relative to baseline of 61.7% *($p < 0.001$)* and 52.4% ($p < 0.001$), respectively. The differences between the one-year and the final evaluation were significant concerning both off- and on-scores *($p = 0.022$* and *$p = 0.002$*, respectively) (Tables 4 and 5).

The tremor scores (item 5 or 6) improved by 96.7% *($p < 0.001$)* after one year and by 91.8% *($p < 0.001$)* at the final evaluation. There were no significant changes in the tremor scores between the first and the final follow-up, except for action tremor where a slight increase from 0.2 ± 0.4 to 0.5 ± 0.6 on-stimulation *($p = 0.034$)* was seen at the final follow-up.

A slight, but still significant, improvement was seen concerning ipsilateral tremor in the on- as compared to the off-state, both after one year and at the final evaluation. The subscores for hand function (items 11–14) of the treated side improved by 90.1% after one year and by 78.0% at the final evaluation. These scores were significantly increased at the final follow-up compared with the 1-year follow-up both on- and off-stimulation.

Items 15–21, which evaluate the activities of daily living (ADL), were improved for on-stimulation by 64.1% *(p < 0.001)* after one year, and by 65 .8% *(p < 0.001)* at the final evaluation.

Item	Maximum Score	Pre-op	One year Stimulation		3–5 years Stimulation	
			Off	On	Off	On
Sum ETRS (item s1–21)	144	46.0 ± 8.7	38.7 ± 4.8*	17.6 ± 8.2**††	45.1.± 16.0#	21.9 ±10.0**††#
Part A (items 1–9)	80	13.5 ± 3.7	10.6 ± 4.8*	5.1 ± 3.1**††	13.0 ± 5.4#	6.9 ± 3.9**††#
Voice tremor (item 3)	4	0.3 ± 0.5	0.1 ± 0.2	0.1 ± 0.2	0.5 ± 0.9#	0.2 ± 0.4
Head tremor (item 4)	8	0.4 ± 0.7	0.2 ± 0.5	0.1 ± 0.3	0.2 ± 0.7	0.1 ± 0.4
Tremor of upper extremity						
ipsilateral to DBS	12	4.4 ± 2.1	4.7 ± 2.7	4.2 ± 2.5†	5.2 ± 2.2	4.5 ± 2.5††
contralateral to DBS	12	6.1 ± 1.8	5.1 ± 2.0*	0.2 ± 0.5**††	4.7 ± 2.3*	0.5 ± 0.8**††
Rest	4	0.4 ± 0.8	0.6 ± 0.8	0.0 ± 0.0*†	0.4 ± 0.6	0.0 ± 0.0**††
Postural	4	2.4 ± 0.9	1.4 ± 0.9*	0.1 ± 0.2**††	1.5 ± 0.8*	0.1 ± 0.2**††
Action/intention	4	3.4 ± 1.0	3.2 ± 0.9	0.2 ± 0.4**††	2.9 ± 1.3	0.5 ± 0.6**††#
Hand function (items 11–14)	32	17.2 ± 4.8	15.2 ± 6.5	8.3 ± 4.2**††	18.5 ± 7.1#	10.5 ± 5.2**††#
Contralateral to DBS	16	9.1 ± 3.2	7.4 ± 3.6	0.9 ± 1.0**††	9.3 ± 4.6#	2.0 ± 2.1**††#
Ipsilateral to DBS	16	7.6 ± 3.3	7.9 ± 3.8	7.5 ± 3.6	8.9 ± 3.7#	8.6 ± 3.8#
ADL (items 15–21)	28	11.7 ± 2.7	11.2 ± 4.6	4.2 ± 4.9**††	12.4 ± 5.4	4.0 ± 3.0**††

.

Table 4) ETRS scores for 18 patients evaluated separately for each of the 20 electrodes before surgery and off/on stimulation at one year and at the final evaluation after 3–5 years (mean 48.5 months). Values are the mean ± standard deviation.

** Significant vs. baseline p ≤ 0.05. ** Significant vs. baseline p ≤ 0.001.*

† Significant vs. off-stimulation p ≤ 0.05. †† Significant vs. off-stimulation p ≤ 0.001.

 # Significant increase since the 1 year follow up p ≤ 0.05.

ETRS = essential tremor rating scale. DBS = deep brain stimulation. ADL = activities of daily living.

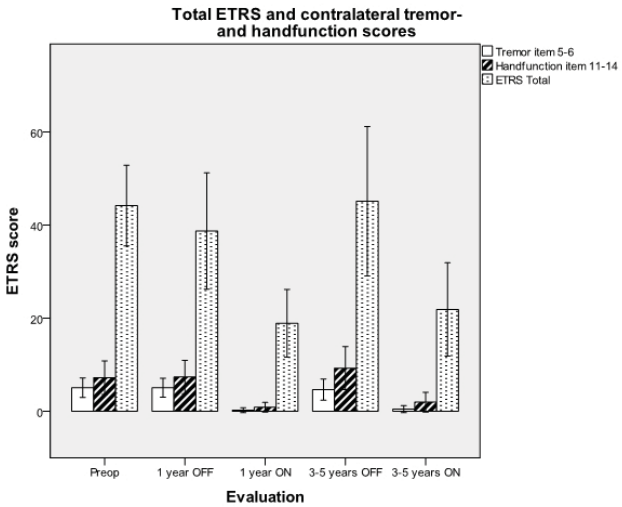


Figure 14) A graph with error bars displaying the total ETRS, the upper extremity tremor and the handfunction scores at the different evaluations.
(Reprinted with permission of the publishers.[224])

Stimulation Parameters

The mean stimulation parameters are presented in Table 6. Pulse effective voltage (PEV) was used as a measurement of stimulation strength ($\sqrt{(U^2 \times pps \times pw}$, where U = voltage (V), pps = pulses per second (Hz), and pw = pulse width (μs)).[80] There were no statistically significant differences in the stimulator settings at any point.

Complications and Battery Replacement

The mainly mild and transient complications that occurred during the first year after surgery have been presented previously.[160] One patient was operated on during the current follow-up with bilateral revision of the extension cables due to strain in the neck. The implantable pulse generator (IPG) was replaced simultaneously, although it was not yet depleted. There were no additional complications or battery replacements during the long-term follow-up.

Item	One year Off	One year On	One year Improvement On (%)	3-5 years Off	3-5 years On	3-5 years Improvement On (%)
Total ETRS	38.7± 4.8	17.6 ± 8.2	**54.5%**	45.1 ± 16.0 #	21.9 ±10.0 #	**51.4%**
Contralat. tremor of upper extr. (item 5/6)	5.1 ± 2.0	0.2 ± 0.5	**96.1%**	4.7 ± 2.3	0.5 ± 0.8	**89.4%**
Contralat. handfunction (item 11-14)	7.4 ± 3.6	0.9 ± 1.0	**87.8%**	9.3 ± 4.6 #	2.0 ± 2.1 #	**78.5%**

Table 5) The on-stimulation scores are compared with the off-scores at each follow up and the improvement in percent with stimulation are shown. Values are mean ± standard deviation.

Significant increase since the 1 year evaluation, $p \leq 0.05$.

	6 weeks	1 year	3–5 years
Mono-/bipolar	14/6	15/5	15/5
Voltage (V)	1.9 ± 0.7	2.4 ± 0.8	2.1 ± 0.6
Pulse-width (μs)	62 ± 7	60± 0	65 ± 11
Frequency (Hz)	166 ± 21	168 ± 21	161 ± 18
Pulse effective voltage (V)	0.20 ± 0.08	0.24 ± 0.08	0.21 ± 0.06

Table 6) Stimulator settings 6 weeks after surgery, at one year, and at the final evaluation after three to five years (mean 48.5 months). Values are the mean ± standard deviation.

Gender & Age	♀ 57*	♂ 59	♂ 58	♂ 66	♂ 61	♂ 78	♂ 63	♂ 59	♂ 70	♂ 62	♀ 62**	♂ 69	♂ 67	♂ 74	♀ 65	Mean
Duration of disease (yr)	16	11	3	2	9	10	2	1	6	7	21	8	3	4	3	**7.1** ± 5.7
L-dopa responder	yes	yes	yes	no	no	no	yes	yes	no	yes	yes	no	yes	yes	yes	**64.3% of all patients**
Microtomy effect	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	no	yes	yes	yes	yes	**93.3% of all patients**
Follow-up (months)	12	50	28	24	24	12	12	16	16	17	12	12	12	12	12	**18.1** ± 10.3
Improvement in percent On-stimulation versus Off-stimulation (%)																**Mean Improvement**
c-lat UPDRS %	64	42	25	*54*	*41*	*65*	70	32	*27*	55	32	*37*	57	61	55	**47.7%**
c-lat Tremor %	100	72	60	*88*	*75*	*88*	100	38	*100*	75	83.3	*73*	100	100	100	**82.2%**
c-lat Rigidity %	60	50	0	*33*	*0*	*25*	67	67	*-25*	20	25	*33*	75	0	-33	**34.3%**
c-lat Brady. %	50	14	11	*39*	*11*	*64*	38	14	*0*	50	0	*13*	17	29	33	**26.7%**

Table 7) Demographic and clinical data for the individual patients in Paper VI. The improvement in percent ON-stimulation versus OFF-stimulation (without medication) is given at the final evaluation for the contralateral (c-lat) subscores of the UPDRS III.
** = The right electrode of the patient undergoing bilateral surgery.*
*** = The left electrode of the patient undergoing bilateral surgery.*
C-lat UPDRS = items 20–26 excl. axial scores. Tremor = 20–21 excl. axial. Rigidity = 22 excl. axial. Bradykinesia = items 23–26.

Paper VI

Fourteen patients were implanted with 15 DBS electrodes using 16 tracks. Clinical and demographic data are presented in Table 7. The minimum follow-up was 12 months (mean 18.1 ± 10.3) and the majority of patients were evaluated within 16 months. Monopolar stimulation was used in 12 cases and the mean stimulation parameters were: amplitude 2.6 V ± 1.0, pulse width 66.0 ± 12.4 µS, and frequency 159.7 ± 26.4 Hz. The medication was 706 ± 425 mg L-dopa equivalents before surgery, and 736 ± 386 mg at last follow-up (p = n.s).

Therapeutic effect

The results regarding UPDRS III are displayed in percent in Table 7 and in absolute scores in Table 8. All but one electrode produced a microtomy effect when introduced in the target, with substantial suppression of tremor which subsided within days to weeks.

Total UPDRS III scores and the rated subscores had increased somewhat from baseline to follow-up. In the following, all comparisons are between on-stimulation/off-medication and the off/off-state, unless indicated otherwise.

Total UPDRS III on stimulation/off medication improved by 32.5% *($p \leq 0.001$)* compared to the off-medication/off-stimulation state. The items of contralateral UPDRS III (cl. UPDRS III), i.e. tremor (items 20–21, excluding tremor of the head), rigidity (item 22, excluding rigidity of the neck), and bradykinesia (items 23–26) were analyzed separately. Total cl. UPDRS III was improved by 47.7% *($p \leq 0.001$)*. Contralateral tremor, rigidity, and bradykinesia were improved by 82.2% *($p \leq 0.001$)*, 34.3% *($p \leq 0.05$)*, and 26.7% *($p \leq 0.001$)*, respectively. Action tremor (item 21) was totally eliminated in 8 of the patients (53.3%) and the mean improved by 80.0% *($p \leq 0.001$)*. Tremor at rest of the arm (item 20b) was totally eliminated in 10 patients (66.7%) and the mean improved by 87.1% *($p \leq 0.001$)*.

The five non-L-dopa responders improved by 82.5% *($p \leq 0.05$)* for tremor, 15.4% *(p =* n.s.) for rigidity and 28.8% *(p =* n.s.) for bradykinesia

One patient had a tremor reduction of only 38% (Table 7). Increasing the amplitude would improve the result, but at the same time affect the contralateral leg. This was probably caused by affection of the internal capsule since the electrode was placed somewhat too laterally. For this reason, the patient had two stimulation settings and could switch between optimal gait with poor tremor control and suboptimal gait with good tremor reduction.

The axial scores (items 18–19, head tremor (20a), neck rigidity (22a) and items 27–30) improved by 19.5% *($p \leq 0.005$)* with stimulation, but no changes were seen concerning the ipsilateral items.

An additive effect was seen on combining stimulation and medication, resulting in an improvement of total UPDRS III of 54%, total cl. UPDRS III, 64%, tremor, 90.4%, rigidity, 68.6%, and bradykinesia, 43.8%.

Location of Active Contacts

The active cathodes were located 12.6 ± 1.4 mm lateral to the midline, 7.0 ± 1.2 mm posterior to the MCP and 2.0 ± 1.8 mm inferior to the intercommissural line (Figure 15).

Adverse Events

As mentioned above, one patient had a suboptimal effect due to stimulation-induced side effects. Another patient suffered an infection at the incision above the burr hole four weeks after surgery. The electrode was explanted and a new one implanted three months later.

Item *(UPDRS item)*	Maximum score	Baseline OFF-med²	Baseline ON-med	Follow-up OFF/OFF	Follow-up ON/OFF	Follow-up OFF/ON	Follow-up ON/ON
UPDRS III (18-31)	114	**37.2** ± 11.4	**26.3** ± 9.3	**46.1** ± 12.1	**29.5** ± 10.5	**31.1** ± 12.9 ††	**21.0** ± 8.4 *††[1]
Cl. UPDRS III (20-26)	36	**17.9** ± 4.3	**12.8** ± 4.9	**21.6** ± 5.4	**14.5** ± 5.1	**11.3** ± 4.3 *††	**7.7** ± 3.2 **††[11]
Cl. Hand tremor at rest (20b)	4	**2.7** ± 0.9	**2.0** ± 1.3	**3.1** ± 1.1	**2.1** ± 1.4	**0.4** ± 0.6 *††[1]	**0.4** ± 0.6 *††[1]
Cl. Action tremor (cl.21)	4	**2.6** ± 1.1	**1.2** ± 1.4	**3.0** ± 1.2	**2.4** ± 1.3	**0.6** ± 0.8 *††[1]	**0.3** ± 0.5 **††[1]
Cl. Tremor (cl.20-21)	12	**5.6** ± 1.9	**3.7** ± 2.8	**7.3** ± 2.4	**4.9** ± 3.0	**1.3** ± 1.5 *††[11]	**0.7** ± 1.0 **††[11]
Cl. Rigidity (cl.22)	8	**3.3** ± 1.3	**2.2** ± 1.0	**3.5** ± 1.6	**2.2** ± 0.6	**2.3** ± 1.2 †	**1.1** ± 0.9 *††[11]
Cl. Bradykin. (cl. 23-26)	16	**8.5** ± 2.8	**6.7** ± 3.6	**10.5** ± 3.1	**7.3** ± 3.2	**7.7** ± 2.9 ††	**5.9** ± 2.3 *††
Axial score (axial 20&22, 18-19,27-30)	32	**7.6** ± 2.8	------	**9.7** ± 3.9	------	**7.7** ± 3.4 ††	------
Ipl. Tremor (ipl.20-21)	12	**3.1** ± 3.3	------	**3.1** ± 3.2	------	**2.2** ± 3.0	------

OFF/OFF = Off-medication/Off-stimulation
ON/OFF = On-medication/Off-stimulation
OFF/ON = Off-medication/On-stimulation
ON/ON = On-medication/On-stimulation

* $p \leq 0.05$ vs. baseline OFF
** $p \leq 0.001$ vs. baseline OFF
† $p \leq 0.05$ vs. OFF/OFF
†† $p \leq 0.001$ vs. OFF/OFF

[1] $p \leq 0.05$ vs. ON/OFF
[11] $p \leq 0.001$ vs. ON/OFF
Cl. = contralateral
Ipl. = Ipsilateral
² 12 pts & 13 sides

Table 8) UPDRS III scores are presented at baseline on/off medication, and on/off medication and stimulation at the follow-up after a mean of 18.1 months. The items of the UPDRS are displayed in parenthesis after the heading in the column to the left. P-values are omitted for on-medication versus off-medication scores. Ipsilateral and axial scores are only displayed in off-medication on/off stimulation. Values are the mean ± standard deviation.

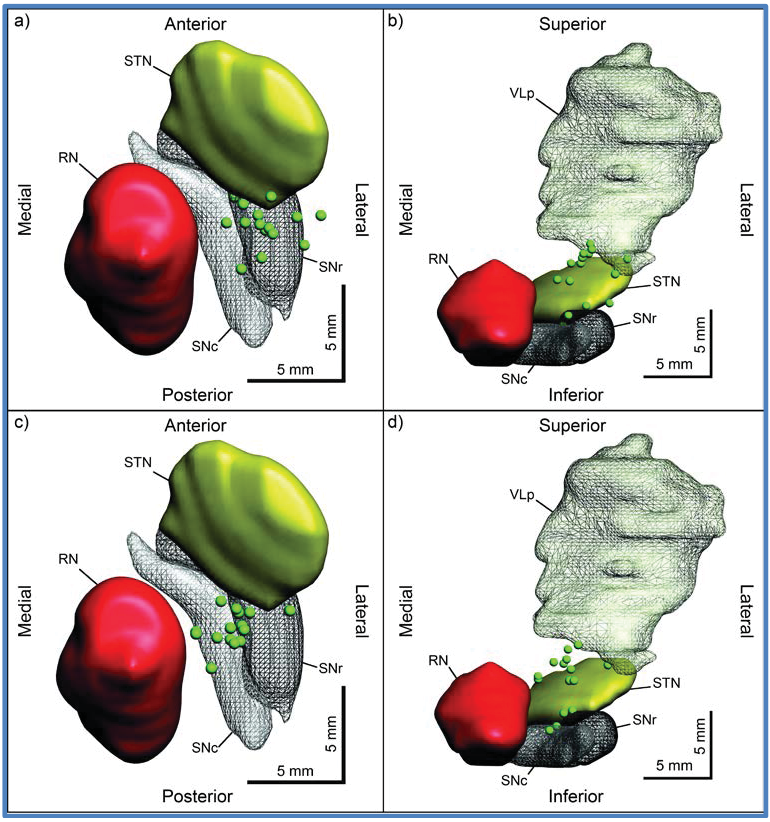


Figure 15) Paper VI: Location of the active electrode contacts used for chronic stimulation in relation to the AC-PC (a and b) and in relation to the posterior tip of the STN (c and d). The figures were made based on the stereotactic atlas of Morel and a 3D atlas was created by using the Matlab 7.0 (The MathWorks, Inc., USA). The location of posterior tip of the STN for Figure c) and d) were set at the level of the maximal diameter of the red nucleus and this was decided from the fused MRI- and postoperative CT-scans. This point corresponds to the posterior tip of the STN on the axial slide "-4.5" in the stereotactic atlas of Morel

Discussion

"The dimensions of the structures in question are so small that significant instrumental errors should not be added to the unavoidable anatomical variations."

- Leksell, L. in "A stereotaxic apparatus for intracerebral surgery 1949".[52]

Part 1: Safety Aspects of DBS in the Posterior Subthalamic Area

Paper I-III,

Side Effects and Complications

The findings are in accord with the limited literature on the subject and indicate that the PSA is safe as a target for DBS. The majority of the encountered complications were mild, the more serious ones being an infection and transient postoperative hemiparesis. The frequency of minor side effects was relatively high, however, compared to previous publications concerning the PSA (Table 1).

With experience from our previous publications on complications after DBS, we speculate whether studies aiming specifically at identifying the side effects of a procedure might be more prone to search for and report complications of minor importance.[111, 112] It is difficult to decide whether this is the case, or if our data simply demonstrate that this procedure is accompanied by a relative high number of minor side effects in our hands.

Papers I and III: Dysphasia and Verbal fluency

Mild transient dysphasia, often detectable only to the patient and not to the examiner, affected 22.5% of the patients in paper I. All but one of these had an electrode in the left hemisphere, half had received two ipsilateral electrodes and all were patients with ET. The dysphasia presented itself before the chronic stimulation was initiated, and it was not increased by the stimulation.

As mentioned in the Introduction, the findings from paper I prompted us to investigate whether it was possible to objectify this by testing verbal fluency as has been done regarding STN and Vim DBS.[115, 281] It was decided to carry out this investigation in patients with ET mainly because of the observations in paper I and also because patients with PD were deemed less suitable since they probably recover more slowly from surgery and might also be affected by changes in L-dopa medication.[280, 282]

As hypothesized, there was a statistically significant tendency in the series towards reduced verbal fluency following cZi DBS as measured immediately after surgery, but after one year the reduction had diminished at the group level and was no longer statistically significant. A sustained reduction was noted nevertheless in individual patients, with the four patients experiencing the most pronounced effect having a reduction of 50% after three days and 38% after one year.

It is well known that the mere introduction of the electrode might have a positive effect on the patient's symptoms. This microlesional effect is often ascribed to the edema evolving around the electrode.[130] However, some patients will have sustained positive effects over longer periods of time as reported in paper IV, suggesting permanent structural lesions. By analogy, we can expect the existence of immediate, as well as of sustained, side effects caused by the same microlesional effects.

The reduction of verbal fluency might be caused either by a microlesion/edema in the cZi, or in other structures along the electrode trajectory.[289] The fact that stimulation of the cZi did not increase the observed effects on verbal fluency might suggest that an influence on other structures may have been responsible. The exact mechanisms underlying thalamic and basal ganglia involvement in verbal fluency are not fully understood. However, in addition to the subthalamic nucleus, other structures such as the caudate nucleus, the centromedian and the Vim nuclei of the thalamus have been implicated as parts of relevant circuits.[290, 291] Dysphasia has not been reported by other groups performing DBS in the cZi or Raprl, but it is common after thalamotomy, occurring in up to 42% of the patients operated in the dominant hemisphere.[207, 209-212, 214, 292-295] There is also data indicating that Vim DBS might have negative effects on verbal fluency.[115, 281] It might thus be suspected that the dysphasia previously seen after cZi DBS, as well as the reduction of verbal fluency in this series, might be caused by the electrode passage through the ventrolateral thalamus situated just above the cZi.

Regarding the laterality of the procedure, it should be noted that since most patients had unilateral left-sided DBS, no conclusions can be drawn regarding the effects of right-sided or bilateral cZi DBS.

The limited size of this series, especially concerning the effects on stimulation, calls for some caution regarding the interpretation of the results. However, the results reported above suggest that cZi DBS is associated with a significant, but transient, effect on verbal fluency. Some patients may display results that indicate a permanent reduction, even though they do not experience any lasting difficulties in finding words. Our observation further suggests that this effect may be caused by microlesional effects/edema related to the trajectory of the electrode rather than by direct effects of stimulation of the cZi.

Finally, it should be noted that the transient dysphasia reported in paper I may of course encompass other components than reductions of verbal fluency capacity. Because of this, it would be important to incorporate broader linguistic tests in future neuropsychological studies on cZi DBS.

Papers I-II: Stimulation-induced side effects

Stimulation-induced side effects in the PSA have only been briefly discussed in a few studies.[126, 197] For other targets used in movement disorders, stimulation-induced side effects are important because they can outline the therapeutic interval for chronic stimulation, and also because intraoperative macrostimulation might provide an indication of the location of the electrode. Sensory side effects, primarily paresthesias, are often not regarded as a major threat to the therapeutic result as there is normally a high degree of habituation over time.

Motor side effects are, however, more often considered to be less susceptible to habituation, and thus more prone to impede the result of the treatment.[278, 279] Reversible stimulation-induced side effects did only impede the clinical result in one patient in Paper I.

The visualizations in paper II demonstrate that different contacts which elicit similar side effects show considerable anatomical variation when plotted on the atlas. This might depend on several factors. Primarily it is of course possible that several distinct anatomical structures in and around the PSA elicit a similar response when stimulated. The axonal predominance of the PSA may also make it more probable that electrical impulses will spread farther than would be expected in predominantly nuclear structures.[276]

Additionally, the interpretation of the anatomical location of coordinates plotted on a stereotactic atlas is not entirely precise due to the individual variability of the central structures of the brain.[296, 297]

Due to the wide distribution of contacts eliciting the same side effects, we find these side effects to be of poor localizing value, and thus of limited importance for orientation during intraoperative macrostimulation.

Motor side effects might be important as mentioned above and separate 3D visualizations (Figure 8a & 8b) were made regarding dysarthria, ataxia, and muscular affection. To test if the impact of interindividual anatomical variations could be reduced, the electrode contacts were plotted not only in relation to the MCP (Figure 8b) but also in relation to the pSTN (Figure 8a), considering its closer relation to the PSA. This reduced the dispersion somewhat, as seen in Figure 8a & 8b, however, not to such an extent that the individual side effect might become of value for localization.

Muscular contractions: Stimulation-induced muscular contractions have been described after Vim and STN DBS. They are normally considered to be caused by affection of the internal capsule (IC).[279] If IC side effects are encountered at subtherapeutic amplitude, a more medial relocation of the electrode should be considered. Contractions of a dystonic phenotype have also been reported and attributed to the STN itself.[278, 279]

During the tests in paper II cramps/tension in an extremity or the face were sometimes clearly visible, but more frequently a discrete dystonic posturing was seen .These side effects probably cannot be ascribed to an affection of the IC. IC-induced cramps in STN DBS are, according to Tommasi et al., most common in the face and occurred in their series at a median amplitude of 4.8 V.[279] One would expect similar features of IC-induced side effects in PSA DBS, however, only in four of the 19 cases were they located in the face, and they appeared as early as at a mean amplitude of 2.6 V (range 1.9–3.3). The contacts causing muscular affection (Figures 8a, b8 & 7) were not, with the exception of one patient, close to the IC. According to Figure 8a and 8b all these contacts were located medial to the pSTN, i.e. not close to the IC.

Dysarthria: Dysarthria is often encountered during DBS. This side effect in Vim and STN DBS has often been interpreted as being caused by too lateral a location of the electrode with affection of the IC.[70, 298-300] While this was true in one patient in our series with a laterally placed electrode, the remaining patients are likely to exhibit this side effect as a consequence of stimulation of the cerebellothalamic fibers in the area, as indicated by previous publications and since their electrodes were placed away from the IC (Figures 8a, 8b, and 7).[301] Dysarthria following STN DBS has recently been shown to be associated with electrodes placed medial to the STN in the cerebellothalamic fibers, whose projections to the Vim might, in some cases, also be involved in dysarthria after Vim DBS.[141, 301-303]

Paresthesias: Paresthesias seem to be elicited throughout the area at relatively low amplitudes and, as seen in Figure 6, there is no clear somatotopic pattern of occurrence.

Other stimulation-induced side effects: Certain cerebellar signs, often reported after subthalamotomies, and which we also observed during evaluation of the stimulation settings, included hypotonia, dysmetria, and disturbance of gait or balance.[136, 189, 199] In one study by Blacker et al., all patients exhibited a postoperative hypotonia combined with slight transient clumsiness of the affected limb after subthalamotomy.[136] Probably, an affection of the same structures explains the two cases of non-stimulation-induced, transient postoperative clumsiness in paper I.

Hypohidrosis due to disruption of sympathetic efferent fibers in the Zi was frequent after subthalamotomies, while DBS in one case has been reported to cause an elevated sympathetic tonus with hyperhidrosis, as in the patient presented in paper I.[203, 205, 304]

Part 2: Therapeutic Effect of DBS in the Posterior Subthalamic Area for the Treatment of Movement Disorders

"Wise men speak because they have something to say, fools because they have to say something."

- Plato

Paper IV–VI

During the lesional era, the PSA was often used as a target for various movement disorders and was considered to be an excellent target for the treatment of tremor. The area was, and is, known to be associated with a pronounced microlesional effect manifested as a substantial or total cessation of tremor when the electrode is introduced in the target.[68-70, 128, 130, 134, 137, 140, 164-166, 197, 223, 228] Until recently, the interest for DBS in this area has been rather limited, but a number of studies have been published during the last few years. In this thesis the effect of PSA/ cZi DBS on several movement disorders with tremor as a dominating symptom was evaluated.

Paper IV: Other forms of tremor

In Paper IV five patients with less common types of tremor were operated on with unilateral DBS in the PSA. Two patients had dystonic-, one primary writing-, one cerebellar-, and one neuropathic tremor. One year after surgery the mean improvement of the targeted tremor and handfunction was 87% on stimulation.
While the mean improvement off-stimulation was 56%, the reduction in the three patients with the most pronounced effect was 89%. In patients 1, 2, and 5, this improvement was interpreted as a sustained microlesional effect, which even allowed for the removal of the IPG in patient 2. Except for one case, this prolonged microlesional effect has not been reported previously after DBS in the PSA, albeit many studies have reported on pronounced microlesional effects of surgery in the PSA as discussed above.[228]

As can be seen in Table 1 in the Introduction, the modern literature on PSA DBS for other forms of tremor than PD and ET mainly consists of one or a few cases regarding each condition. However, these papers do report favorable therapeutic result for this heterogeneous group of movement disorders.[197, 221, 223, 228]
The results from Paper IV are also promising concerning PSA DBS for less common forms of tremor. The existing published material is of limited size, however, and our series was small.

Paper V: Essential tremor

Therapeutic effect: Paper V evaluated 18 patients treated with cZi DBS for ET after a mean of 4 years. The baseline total ETRS score of 46.0 was decreased to 21.9 (*52.4%*) at the final evaluation. On the treated side, tremor of the upper extremity improved by *91.8%* and hand function (items 11–14) improved by *78.0%*. The ADL scores improved by 65.8%.

The improvement without stimulation, the microlesional effect, which still was evident 1 year after surgery, had to a large extent veined at the last follow up. There was also some degree of decreased improvement on-stimulation compared to the one-year results. This is probably to a large extent due to a reduced microlesional effect and progression of tremor.

This assumption is supported by a previous study which indicated that the more tremor a patient had off-stimulation, the more residual tremor the patient would have on-stimulation.[229] Furthermore, with the exception of action tremor, all significant increases from 1 year to the final evaluation on-stimulation were accompanied by corresponding increases off-stimulation. Neither was any late treatment failures observed in this population. Considering these facts, development of tolerance seems to have been limited. This is further supported by the lack of increase regarding stimulation parameters, as discussed below

Previous reports concerning the long-term effects of PSA DBS are limited to four patients with bilateral implants, in whom the total ETRS score was improved by 72.6% after a follow-up of four years or more.[220] As discussed above, thalamic DBS of the Vim nucleus is at present regarded as the standard target for ET. With regard to the long-term studies on Vim DBS, it is often difficult to compare different ones, because many involve mixed bilateral and unilateral procedures and because the ETRS data are presented in various ways. The European and American multicenter studies with 5–6 year follow-ups reported 50–75% tremor reduction in the treated arm after unilateral VIM DBS[100, 305] In our own experience of 19 cases with Vim DBS evaluated at a mean of seven years after surgery, the tremor of the contralateral upper extremity was reduced by 60.3% and hand function was improved by 35.4%.[124]

Energy consumption: The PEV remained practically unchanged (0.20 vs. 0.21 V) and no batteries were replaced due to depletion during the follow-up of up to 5 years. In our long-term study of Vim DBS, the PEV increased from 0.15 after one month to 0.24 V after five years and to 0.29 V after seven years.[124] Other long-term studies of Vim DBS report values of 0.27–0.48 and the PEV was 0.36 for the four patients with long-term cZi DBS reported by Plaha et al.[80, 100, 305-307]

PSA DBS for ET: Development of tolerance to stimulation over time, making it necessary to increase the stimulation parameters and also, in some cases, causing stimulation failure, is reported quite frequently after Vim DBS for ET.[124, 306, 308-311] This can be a major problem, and Plaha et al. have suggested that it might be due to properties of the Vim itself.[220] . No late treatment failures were observed among the patients in paper V and the long-lasting treatment effects of cZi DBS appear to be achieved at a low stimulation strength compared to other reports and without any apparent development of tolerance. In summary, this long-term follow-up of 18 patients indicates that cZi DBS is a safe and effective treatment for ET – also in the long run.

Paper VI: Parkinsonian tremor:

In Paper VI 14 patients with predominately unilateral tremor-dominant PD and insufficient relief from pharmacologic therapy were operated on with unilateral cZi DBS and one patient underwent a bilateral staged procedure. Five of the patients had non-L-dopa responsive symptoms. At the follow-up after a mean of 18.1 months, stimulation in the off-medication state improved the contralateral UPDRS III score by 47.7%. Contralateral tremor, rigidity, and bradykinesia were improved by 82.2%, 34.3%, and 26.7%, respectively. Stimulation alone also abolished tremor at rest in 66.7% and action tremor in 53.3% of the patients.

The results in paper VI demonstrated satisfying efficacy and safety of cZi DBS for Parkinsonian tremor and adds to the growing body of knowledge indicating this target as a promising alternative in Parkinsonian tremor. The level of tremor reduction presented in this series is in line with previous reports and it is also notable that this effect seemed to be equally good for non-L-dopa responders.[126, 141, 165, 220, 221, 225, 227]

The effects on rigidity and bradykinesia were, however, less positive than previously reported by other groups. Previous studies on PSA DBS reported improvement of

contralateral tremor by 78%–93%, rigidity by 45%–94%, and bradykinesia by 46%–75% (Table 1 in the Introduction).[126, 141, 165, 220, 221, 225, 227]

The optimal target within the PSA is not known; however, the coordinates of our active contacts were close to those reported by other groups, as seen in Table 1, and the 3D reconstructions with the active cathodes shown in Figure 15 seem to be in line with other authors´ publications.

Perhaps the fact that a third of our patients had non-L-dopa responsive symptoms and that the severity of rigidity and bradykinesia was rather limited in comparison to the severity of tremor in many patients contributed to the limited effect of cZi DBS on non-tremor PD symptoms.

Vim DBS and STN DBS are the other alternative targets for DBS in tremor-dominant PD. The European Multicenter Study reported improvements of 75% for tremor, 23% for rigidity, and 35% for bradykinesia in 57 patients after unilateral Vim DBS.[98] The effect on tremor did not appear to decline at the long-term follow-up after 6 years as has been reported concerning Vim stimulation for ET.[99, 124] The analysis of the effect of Vim DBS may, however, be somewhat complicated as the electrode can be advanced into the PSA during surgery, and the contact stimulated in "Vim DBS" may well be located ventral to the thalamus in the subthalamic area, as has been shown in several studies.[237-240]

The effects of bilateral STN DBS on PD symptoms are well known, and some studies have focused on the effects in patients with severe tremor, where a tremor reduction of 80–84% has been reported.[312, 313] The literature on the effect of unilateral STN DBS specifically for patients with tremor-dominant PD seems to be very limited, however. Two papers (34 patients) that specified the improvement of the different motor symptoms following unilateral STN DBS were identified. The follow-up was short (7–9 months), and the severity of tremor at baseline was low (60% lower than in our series). Nevertheless, contralateral tremor improved by 86–88%, rigidity by 31–60%, and bradykinesia by 30–54%.[314, 315]

In summary, cZi DBS seems to be a safe and effective target for the treatment of tremor-dominant hemi-Parkinsonism, but the effect on rigidity and bradykinesia in Paper VI was less profound than previously reported for PSA DBS in PD. Further studies are needed before we will know how the relative merits of different DBS targets can be used to tailor the treatment for the individual patient with PD.

"If I have ever made any valuable discoveries, it has been due more to patient attention, than to any other talent."

- *Sir Isaac Newton*

General summary: DBS of the PSA in the treatment of movement disorders

PSA DBS was accompanied by few serious side effects in this series, but an immediate, transient, and mild postoperative dysphasia was detected for some patients. The relationship between PSA DBS and language functions was further supported by a slightly reduced verbal fluency following surgery. The material was, however, limited and more detailed neuropsychological evaluations are warranted. Dysphasia or declines in verbal fluency have been reported both following Vim and STN DBS.[115, 280-282] These targets are located in the absolute proximity of the PSA. Considering this, it is perhaps not surprising, that one finds similar side effects for PSA DBS. It is however also possible, that these side effects have a closer relationship to DBS for movement disorders in general, than to the targeted substructure or the electrode trajectory. We can conclude, that our results indicate a possible relationship between PSA DBS and mild declines in the ability to produce language. We can also conclude that broader linguistic and neuropsychological studies are needed before we can decide on the relevance of these findings.

The investigations could not provide a meaningful somatotopic map for the stimulation-induced side effects in the PSA. Whether this was due to poor methodological design, or not, is difficult to answer. Stimulation-induced muscular affection and dysarthria did normally not seem to be of capsular origin. These side effects, as well as paresthesias tended to fade out and were seldom a threat to the therapeutic result.

It is interesting, that for example dysarthria, can be elicited from more or less the same point within the PSA as from which a good clinical effect is achieved. Considering this, and the fading nature of the side effects described above, it seems as if the therapeutic effect and verification of the anatomic position of the electrode might be more important than evaluating intraoperative side effects. If the electrode has a good location within the PSA, possible stimulation-induced side effects seem to fade out. This has implications regarding the possibility of performing these operations under general anesthesia. More knowledge about the physiology of the PSA can hopefully be gathered with the use of new techniques such as functional MRI, directed stimulation fields and diffusion tensor imaging (DTI).

In summary, regarding the safety of PSA DBS, it has been suggested that lesional procedures in the PSA were discarded due to the side effects associated with the procedure.[196, 197] This is not evident from the literature. Nor is it clear that the attempts to compare subthalamotomies, thalamotomies, and combinations of these, have demonstrated either procedure to be preferable in regard to safety.[153, 163, 178, 199]

With regard to DBS, the investigations in this thesis do not give the impression that the PSA is a less safe target than the Vim or STN.

The findings in this thesis favor the notion that the PSA, including the cZi and the Raprl, is an effective target for DBS in movement disorders with tremor as a dominating symptom. Tremor of various types such as ET, PD, dystonic, writing, and cerebellar tremor all responded well to the treatment. The microlesional effect for the ET patients was still statistical significant after 1 year. The long-term effectiveness and energy consumption for cZi DBS in ET was satisfying. cZi DBS was effective on Parkinsonian tremor, also for patients with non L-dopa responsive PD. The improvement on all forms of tremor was

comparable to previous publications of PSA DBS.[3, 126, 141, 160, 165, 196, 220-223, 228] For ET, the long term effectiveness was positive compared to our previous results of Vim DBS, and the results were also good compared to other publications of Vim DBS.[100, 124, 197, 220-222, 305]

For Parkinsonian tremor, the effects were comparable to other publications of PSA, Vim and STN DBS.[98, 126, 141, 165, 221, 225, 227, 314, 315] With regard to rigidity and bradykinesia, the effects were not as positive as reported in the few papers on PSA DBS that exists.[126, 141, 165, 221, 225, 227] On the other hand, the effects did not differ much from what mostly has been reported for unilateral Vim and STN DBS.[98, 314, 315] We should remember that the patients in paper VI did not have severe rigidity and bradykinesia. More studies are needed to investigate the role of PSA DBS in PD.

The findings in this thesis are generally in line with the existing literature on PSA DBS and also coherent with the knowledge of the PSA from the lesional era. The modern literature is however limited, and the literature from the lesional area is difficult to interpret due to the differing ways of presenting the data.[3] Nevertheless, several factors indicate that the PSA is a key point within the circuits that transmit tremor to the motor thalamus. Whether this is because of the denseness of cerebello-thalamic fibers, due to the properties of the cZi, a combination of these, or any other factor still remains to be decided.[221, 240, 243, 261]

A good location in the PSA can often be reached just by advancing a few millimeters below the Vim when using the same trajectory as one would when targeting Vim.[160] Accumulating data supports the effectiveness of PSA DBS for tremor-dominant disorders, and studies of the optimal contact location in Vim DBS has indicated that this actually might be below Vim, within the PSA.[240, 241]

The PSA should be further evaluated as a target for tremor-dominant movement disorders, ideally in randomized controlled studies comparing this target to Vim and STN.

Conclusions

• DBS of the posterior subthalamic area seems safe and was accompanied by few serious side-effects.

• A mild and transient dysphasia that was not stimulation induced was encountered in several patients with ET.

• An immediate and partly transient decline of verbal fluency that was not affected by stimulation was seen in patients with ET.

• Stimulation-induced side effects in the PSA were of limited localizing value and posed few problems in these series of PSA DBS.

• Dysarthria and muscular affection do in most cases not seem to be elicited by spread to the internal capsule when stimulating the PSA.

• The effect on the more uncommon forms of tremor, such as dystonic, cerebellar, and writing tremor, was satisfying and the microlesional effect alone improved several patients substantially.

• The long-term effectiveness and energy consumption for cZi DBS in ET were satisfying and also favorable compared to our previous results of Vim DBS.

• cZi DBS was effective for tremor-dominant Parkinson's disease although the effect on rigidity and bradykinesia was less than reported previously.

Acknowledgements

"If I have seen further it is by standing on the shoulders of giants."

- Sir Isaac Newton, 1676

I wish to express my most humble and sincere gratitude to all co-authors and all those who have supported me during the writing of this thesis. I especially wish to thank:

Associate Professor Patric Blomstedt, for being the best supervisor I could ever imagine.

Professor Tommy Bergenheim, my co-supervisor, for encouraging and convincing me that "everything´s gonna be all right."

Professor Marwan Hariz, for being a role model in the "World of Functional and Stereotactic Neurosurgery" and gracefully passing on the legacy of Lauri Laitinen to this department.

Associate Professor Lars-Owe Koskinen, for valuable advice and encouragement

Magnus Olivecrona, MD, PhD, for honest advice and for believing in me.

Anna Fredricks, R.N., for your help and skillful management of the patients in this thesis

Jan Linder, MD, and the DBS team for your support.

Kerstin Gruffman, for guiding me through the "bureaucratic jungle" with optimism.

All my colleagues at the Department of Neurosurgery at the Karolinska University Hospital in Stockholm for facilitating this work in every way.

Mattias Åström, MSc and PhD in Biomedical Engineering for his ideas and excellent collaboration.

Lina Gustin and Mattias Hägglund, for your unconditional hospitality and for thereby making this work possible at all.

Peter Alpkvist, MD, for your friendship and support in the sometimes frustrating life of the resident in neurosurgery.

Jonas Frodlund, MD, my dear friend and colleague, for dragging me thorough my first and futile attempt at scientific work.

My mother, Betty Engdahl, for your support and for inspiring me to be thoughtful.

My father, Peter Engdahl, for your support and for teaching me to never give up.

My beloved, wife Isa Gustin, to whom my gratitude is indescribable.

References

1. Wikipedia. *Coord-system-CA 0.* 2009; Available from: http://en.wikipedia.org/wiki/File:Coord_system_CA_0.svg.
2. Laitinen LV, Personal memories of the history of stereotactic neurosurgery. *Neurosurgery,* 2004. **55**(6): p. 1420-9.
3. Blomstedt P, U Sandvik, A Fytagoridis, et al., The posterior subthalamic area in the treatment of movement disorders: past, present, and future. *Neurosurgery,* 2009. **64**(6): p. 1029-38; discussion 38-42.
4. Gildenberg PL, History repeats itself. *Stereotact Funct Neurosurg,* 2003. **80**(1-4): p. 61-75.
5. Suss RA, Stereotactic versus stereotaxic. *Neurosurgery,* 1993. **33**(6): p. 1114.
6. Gildenberg PL, Stereotactic versus stereotaxic. *Neurosurgery,* 1993. **32**(6): p. 965-6.
7. Benabid AL, P Pollak, A Louveau, et al., Combined (thalamotomy and stimulation) stereotactic surgery of the VIM thalamic nucleus for bilateral Parkinson disease. *Appl Neurophysiol,* 1987. **50**(1-6): p. 344-6.
8. Remy M, M Contremoulins, Le chercheur de projectiles. *L'illustration,* 1897. **55**: p. 423.
9. Horsley V, R Clarke, The structure and functions of the cerebellum examined by a new method. *Brain,* 1908. **31**: p. 45-124.
10. Blomstedt P, M Olivecrona, A Sailer, et al., Dittmar and the history of stereotaxy; or rats, rabbits, and references. *Neurosurgery,* 2007. **60**(1): p. 198-201; discussion 01-2.
11. Benabid AL, Quelques considérations sur l'histoire de la stéréotaxie. *Rev Neurol (Paris),* 1999. **155**(10): p. 869-77.
12. Zernov D, Encephalometer: Device for estimation of parts of brain in humans. *Proc Soc Physicomed Moscow Univ,* 1889. **2**: p. 70-80.
13. Picard C, A Olivier, G Bertrand, The first human stereotaxic apparatus. The contribution of Aubrey Mussen to the field of stereotaxis. *J Neurosurg,* 1983. **59**(4): p. 673-6.
14. Kandel EI, YV Shchavinskii, First stereotaxic apparatus created by Russian scientists in the 19th century. *Biomed Eng (NY),* 1973. **7**(2): p. 121-4.
15. Spiegel EA, HT Wycis, M Marks, et al., Stereotaxic apparatus for operations on the human brain. *Science,* 1947. **106**: p. 349-50.
16. Spiegel E, HT Wycis**,** Stereoencephalotomy: I. Methods and stereotaxic atlas of the human brain. 1952, New York: Grune & Stratton.
17. Gildenberg PL, History of Stereotactic surgery in Textbook of Stereotactic and Functional Neurosurgery Lozano AM, Gildenberg PL, and Tasker RR, Editors. 2009, Springer-Verlag: Berlin-Heidelberg. p. 3-33.
18. Dandy WE, Ventriculography following the injection of air into the cerebral ventricles. *Ann Surg,* 1918. **68**: p. 5-11.
19. Hariz MI, Comment on "The posterior subthalamic area in the treatment of movement disorders: past, present, and future". *Neurosurgery,* 2009. **64**(6): p. 1040-41.
20. Gildenberg PL, Spiegel and Wycis - the early years. *Stereotact Funct Neurosurg,* 2001. **77**(1-4): p. 11-6.
21. Spiegel EA, History of Human Stereotaxy, in Stereotaxy of the human brain., Schaltenbrand G and Walker AE, Editors. 1982, Georg Thieme Verlag: Stuttgart/New York. p. 3-10.

22. Laitinen LV, Surgical treatment, past and present, in Parkinson's disease. *Acta Neurol Scand Suppl,* 1972. **51**: p. 43-58.
23. Gildenberg PL, Stereotactic surgery--the past and the future. *Stereotact Funct Neurosurg,* 1998. **70**(2-4): p. 57-70.
24. Redfern RM, History of stereotactic surgery for Parkinson's disease. *Br J Neurosurg,* 1989. **3**(3): p. 271-304.
25. Horsley V, The function of the so-called motor area of the brain. *Br Med J,* 1909. **2**: p. 125-32.
26. Gabriel EM, BS Nashold, Jr., Evolution of neuroablative surgery for involuntary movement disorders: an historical review. *Neurosurgery,* 1998. **42**(3): p. 575-90.
27. Bucy PC, Cortical extirpation in the treatment of involuntary movements. *Am J Surg,* 1948. **75**: p. 257-63.
28. Browder J, Section of the fibers of the anterior limb of the internal capsule in Parkinsonism. *Am J Surg,* 1948. **75**: p. 264-68.
29. Bucy PC, Cortical extirpation in the treatment of involuntary movements. *Res Publ Assoc Res Nerv Ment Dis,* 1942. **21**: p. 551-95.
30. Parrent AG, History of Surgery for Movement Disorders, in Textbook of stereotactic and functional neurosurgery, Lozano AM, Gildenberg PL, and Tasker RR, Editors. 2009, Springer-Verlag: Berlin-Heidelberg. p. 1467-85.
31. Meyers R, Historical background and personal experience in the surgical relief of hyperkinesia and hypertonus, in Pathogenesis and Treatment of Parkinsonism, Fields W, Editor. 1958, Springfield: Thomas. p. 229-70.
32. Dandy WE, Changes in our conceptions of localization of certain functions in the brain. *Am J Physiol,* 1930. **93**: p. 643-7.
33. Guiot G, J Pecker, Tractotomie mésencéphalic antérieure pour tremblement parkinsonien. *Rev Neurol,* 1949. **81**: p. 387-9.
34. Cooper IS, Ligation of the anterior choroidal artery for involuntary movements of parkinsonism. *Psychiatr Q,* 1953. **27**: p. 317-9.
35. Cooper IS, Surgical occlusion of the anterior choroidal artery in parkinsonism. *Surg Gynecol Obstet,* 1954. **92**(2): p. 207-19.
36. Cooper IS, Surgical alleviation of Parkinsonism; effects of occlusion of the anterior choroidal artery. *J Am Geriatr Soc,* 1954. **2**(11): p. 691-718.
37. Cooper IS, LL Bergmann, A Caracalos, Anatomic Verification of the Lesion Which Abolishes Parkinsonian Tremor and Rigidity. *Neurology,* 1963. **13**: p. 779-87.
38. Guridi J, AM Lozano, A brief history of pallidotomy. *Neurosurgery,* 1997. **41**(5): p. 1169-80.
39. Meyers R, The human frontocorticopontine tract: functional inconsequence of its surgical interruption. *Neurology,* 1951. **1**: p. 341-56.
40. Guiot G, S Brion, Traitement de mouvements anormaux par la coagulation pallidale. Technique et résultats. *Rev Neurol,* 1953. **89**: p. 578-80.
41. Fenelon F, Essai de traitement neurochirurgical du syndrome parkinsonien par intervention directe sur les voies extrapyramidales immediatement sous-striopallidales (anse lenticulaires). *Rev Neurol (Paris),* 1950. **83**(5): p. 437-40.
42. Hamby WB, Parkinsonism: Is it a surgical problem? *N Y State J Med,* 1947. **47**: p. 2592.
43. Talairach JH, M. David, M. Monnier, M. Ajuriaguerra, J., Recherches sur la coagulation therapeutique des structures sous-corticales chez l'homme. *Rev Neurol,* 1949. **8**: p. 4-24.
44. Riechert T, Development of human stereotactic surgery. *Confin Neurol,* 1975. **37**(4): p. 399-409.

45. Mark VH, PP McW, H Sweet, A new method for correcting distortion in cranial roentgenograms, with special reference to a new human stereotactic instrument. *Am J Roentgenol Radium Ther Nucl Med,* 1954. **71**(3): p. 435-44.
46. Jasper H, G Bertrand, Stereotaxic microelectrode studies of single thalamic cells and fibres in patients with dyskinesia. *Trans Am Neurol Ass,* 1964. **89**: p. 79-82.
47. Bertrand C, N Martinez, An apparatus and technique for surgery of dyskinesias. *Neurocirugia,* 1959. **2**: p. 36-46.
48. Austin G, A Lee, A plastic ball-and-socket type of stereotaxic director. *J Neurosurg,* 1958. **15**(3): p. 264-8.
49. Bailey PS, SN**.,** A stereotaxic apparatus for use on the human brain. 1951, Atlantic City: AMA Scientific Exhibit.
50. Cooper I, Chemopallidectomy. *Science,* 1955. **121**: p. 217-8.
51. Cooper IS, Intracerebral injection of procaine into the globus pallidus in hyperkinetic disorders. *Science,* 1954. **119**(3091): p. 417-8.
52. Leksell L, A stereotaxic apparatus for intracerebral surgery. *Acta Chir Scand,* 1949. **99**: p. 229-33.
53. Nashold BS, The history of stereotactic neurosurgery. *Stereotact Funct Neurosurg,* 1994. **62**(1-4): p. 29-40.
54. Rand RW, A stereotaxic instrument for pallidothalamectomy in Parkinson's disease. *J Neurosurg,* 1961. **18**: p. 258-60.
55. Riechert TW, M., Über ein neues Zielgerät zur intrakraniellen elektrischen Abteilung und Ausschaltung. *Arch Psychiat Z Neurol,* 1951. **186**: p. 225-30.
56. Uchimura Y, H Narabayashi, Stereoencephalotom*.* *Psychiat Neurol Jap,* 1951. **52**: p. 265.
57. Meyerson BA, B Linderoth, Histroy of Stereotactic Neurosurgery in the Nordic Countries, in Textbook of Functional and Stereotactic Neurosurgery, Lozano AM, Gildenberg PL, and Tasker RR, Editors. 2009, Springer-Verlag: Berlin-Heidelberg.
58. Spiegel EA, HT Wycis, HW Baird, 3rd, Long-range effects of electropallidoansotomy in extrapyramidal and convulsive disorders. *Neurology,* 1958. **8**(10): p. 734-40.
59. Riechert T, Long term follow-up of results of stereotaxic treatment in extrapyramidal disorders. *Confin Neurol,* 1962. **22**: p. 356-63.
60. Mundinger F, T Riechert, [The stereotactic brain operations for the treatment of extrapyramidal movement disorders (parkinsonism and hyperkinesias) and their results]. *Fortschr Neurol Psychiatr,* 1963. **31**: p. 69-120 concl.
61. Spiegel EA, Methodological problems in stereoencephalotomy. *Confin Neurol,* 1965. **26**(3): p. 125-32.
62. Cooper IS, Procaine injection of the globus pallidus in Parkinsonism*.* *Psychiatr Q,* 1954. **28**(1): p. 22-3.
63. Narabayashi H, T Okuma, Procaine oil blocking of the globus pallidus for the treatment of rigidity and tremor of parkinsonism. *Proc JPN Acad,* 1953. **29**: p. 310-18.
64. Hassler R, T Riechert, [Indications and localization of stereotactic brain operations.]. *Nervenarzt,* 1954. **25**(11): p. 441-7.
65. Svennilson E, A Torvik, R Lowe, et al., Treatment of parkinsonism by stereotatic thermolesions in the pallidal region. A clinical evaluation of 81 cases. *Acta Psychiatr Scand,* 1960. **35**: p. 358-77.
66. Mundinger F, Results of 500 subthalamotomies in the region of the zona incerta, in Third symposium on Parkinson's disease. 1969, E & S Livingstone: Edinburgh and London. p. 261-5.

67. Andy OJ, MF Jurko, FR Sias, Subthalamotomy in the treatment of Parkinson tremor. *Thirty-first annual meeting of the Harvey Cushing society,* 1963: p. 46.
68. Andy OJ, MF Jurko, FR Sias, Subthalamotomy in treatment of Parkinsonian tremor. *J Neurosurg,* 1963. **20**: p. 860-70.
69. Bertrand C, Localization of lesions. *J Neurosurg,* 1966. **24**: p. 446-8.
70. Bertrand C, J Hardy, P Molina-Negro, et al., Optimum physiological target for the arrest of tremor, in Third symposium on Parkinson's diease, Gillingham FJ and Donaldson IML, Editors. 1969, Livingstone, E.S.: Edinburgh. p. 251-59.
71. Wertheimer P, J Bourret, C Lapraz, [Apropos of the treatment of a dyskinesia by stereotaxic leucotomy.]. *Rev Neurol,* 1960. **102**: p. 481-6.
72. Hassler R, T Riechert, F Mundinger, et al., Physiological observations in stereotaxic operations in extrapyramidal motor disturbances. *Brain,* 1960. **83**: p. 337-50.
73. Krayenbuhl H, OA Wyss, MG Yasargil, Bilateral thalamotomy and pallidotomy as treatment for bilateral Parkinsonism. *J Neurosurg,* 1961. **18**: p. 429-44.
74. Carlsson A, M Lindqvist, T Magnusson, et al., On the presence of 3-hydroxytyramine in brain. *Science,* 1958. **127**(3296): p. 471.
75. Cotzias GC, MH Van Woert, LM Schiffer, Aromatic amino acids and modification of parkinsonism. *N Engl J Med,* 1967. **276**(7): p. 374-9.
76. Carlsson A, M Lindqvist, T Magnusson, 3,4-Dihydroxyphenylalanine and 5-hydroxytryptophan as reserpine antagonists. *Nature,* 1957. **180**(4596): p. 1200.
77. Gildenberg PL, Whatever happened to stereotactic surgery? *Neurosurgery,* 1987. **20**(6): p. 983-7.
78. Laitinen LV, Brain targets in surgery for Parkinson's disease. Results of a survey of neurosurgeons. *J Neurosurg,* 1985. **62**(3): p. 349-51.
79. Laitinen LV, AT Bergenheim, MI Hariz, Leksell's posteroventral pallidotomy in the treatment of Parkinson's disease. *J Neurosurg,* 1992. **76**(1): p. 53-61.
80. Rehncrona S, B Johnels, H Widner, et al., Long-term efficacy of thalamic deep brain stimulation for tremor: double-blind assessments. *Mov Disord,* 2003. **18**(2): p. 163-70.
81. Krack P, A Batir, N Van Blercom, et al., Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. *N Engl J Med,* 2003. **349**(20): p. 1925-34.
82. Krack P, L Vercueil, Review of the functional surgical treatment of dystonia. *Eur J Neurol,* 2001. **8**(5): p. 389-99.
83. Limousin P, I Martinez-Torres, Deep brain stimulation for Parkinson's disease. *Neurotherapeutics,* 2008. **5**(2): p. 309-19.
84. Benabid AL, A Benazzouz, D Hoffmann, et al., Long-term electrical inhibition of deep brain targets in movement disorders. *Mov Disord,* 1998. **13 Suppl 3**: p. 119-25.
85. Benabid AL, S Chabardes, J Mitrofanis, et al., Deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease. *Lancet Neurol,* 2009. **8**(1): p. 67-81.
86. Benabid AL, S Chabardes, E Seigneuret, et al., Surgical therapy for Parkinson's disease. *J Neural Transm Suppl,* 2006(70): p. 383-92.
87. Benabid AL, G Deuschl, AE Lang, et al., Deep brain stimulation for Parkinson's disease. *Mov Disord,* 2006. **21 Suppl 14**: p. S168-70.
88. Benabid AL, A Koudsie, A Benazzouz, et al., Subthalamic stimulation for Parkinson's disease. *Arch Med Res,* 2000. **31**(3): p. 282-9.
89. Benabid AL, P Pollak, C Gervason, et al., Long-term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus. *Lancet,* 1991. **337**(8738): p. 403-6.

90. Benabid AL, P Pollak, E Seigneuret, et al., Chronic VIM thalamic stimulation in Parkinson's disease, essential tremor and extra-pyramidal dyskinesias. *Acta Neurochir Suppl (Wien),* 1993. **58**: p. 39-44.
91. Benabid AL, L Vercucil, A Benazzouz, et al., Deep brain stimulation: what does it offer? *Adv Neurol,* 2003. **91**: p. 293-302.
92. Pollak P, AL Benabid, C Gross, et al., Effects of the stimulation of the subthalamic nucleus in Parkinson disease. *Rev Neurol (Paris),* 1993. **149**(3): p. 175-6.
93. Pollak P, AL Benabid, P Limousin, et al., Subthalamic nucleus stimulation alleviates akinesia and rigidity in parkinsonian patients. *Adv Neurol,* 1996. **69**: p. 591-4.
94. Pollak P, AL Benabid, P Limousin, et al., Treatment of Parkinson's disease. New surgical treatment strategies. *Eur Neurol,* 1996. **36**(6): p. 400-4.
95. Siegfried J, B Lippitz, Bilateral chronic electrostimulation of ventroposterolateral pallidum: a new therapeutic approach for alleviating all parkinsonian symptoms. *Neurosurgery,* 1994. **35**(6): p. 1126-9.
96. Siegfried J, B Lippitz, Chronic electrical stimulation of the VL-VPL complex and of the pallidum in the treatment of movement disorders: personal experience since 1982. *Stereotact Funct Neurosurg,* 1994. **62**(1-4): p. 71-5.
97. Deuschl G, C Schade-Brittinger, P Krack, et al., A randomized trial of deep-brain stimulation for Parkinson's disease. *N Engl J Med,* 2006. **355**(9): p. 896-908.
98. Limousin P, JD Speelman, F Gielen, et al., Multicentre European study of thalamic stimulation in parkinsonian and essential tremor. *J Neurol Neurosurg Psychiatry,* 1999. **66**(3): p. 289-96.
99. Hariz MI, P Krack, F Alesch, et al., Multicentre European study of thalamic stimulation for parkinsonian tremor: a 6 year follow-up. *J Neurol Neurosurg Psychiatry,* 2008. **79**(6): p. 694-9.
100. Sydow O, S Thobois, F Alesch, et al., Multicentre European study of thalamic stimulation in essential tremor: a six year follow up. *J Neurol Neurosurg Psychiatry,* 2003. **74**(10): p. 1387-91.
101. Follett KA, Comparison of pallidal and subthalamic deep brain stimulation for the treatment of levodopa-induced dyskinesias. *Neurosurg Focus,* 2004. **17**(1): p. E3.
102. Follett KA, FM Weaver, M Stern, et al., Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. *N Engl J Med,* 2010. **362**(22): p. 2077-91.
103. Benabid AL, P Pollak, C Gross, et al., Acute and long-term effects of subthalamic nucleus stimulation in Parkinson's disease. *Stereotact Funct Neurosurg,* 1994. **62**(1-4): p. 76-84.
104. Limousin P, P Pollak, A Benazzouz, et al., Bilateral subthalamic nucleus stimulation for severe Parkinson's disease. *Mov Disord,* 1995. **10**(5): p. 672-4.
105. Limousin P, P Pollak, A Benazzouz, et al., Effect of parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation. *Lancet,* 1995. **345**(8942): p. 91-5.
106. Pahwa R, KE Lyons, SB Wilkinson, et al., Comparison of thalamotomy to deep brain stimulation of the thalamus in essential tremor. *Mov Disord,* 2001. **16**(1): p. 140-3.
107. Yap L, A Kouyialis, TR Varma, Stereotactic neurosurgery for disabling tremor in multiple sclerosis: thalamotomy or deep brain stimulation? *Br J Neurosurg,* 2007. **21**(4): p. 349-54.
108. Schuurman PR, DA Bosch, MP Merkus, et al., Long-term follow-up of thalamic stimulation versus thalamotomy for tremor suppression. *Mov Disord,* 2008. **23**(8): p. 1146-53.
109. Blomstedt P, Analysis of deep brain stimulation and ablative lesions in surgical treatment of movement disorders - with emphasis on safety aspects. *Thesis University of Umeå,* 2007: p. April.

110. Blomstedt P, GM Hariz, MI Hariz, Pallidotomy versus pallidal stimulation. *Parkinsonism Relat Disord,* 2006. **12**(5): p. 296-301.
111. Blomstedt P, MI Hariz, Are complications less common in deep brain stimulation than in ablative procedures for movement disorders? *Stereotact Funct Neurosurg,* 2006. **84**(2-3): p. 72-81.
112. Blomstedt P, MI Hariz, Hardware-related complications of deep brain stimulation: a ten year experience. *Acta Neurochir (Wien),* 2005. **147**(10): p. 1061-4.
113. Jimenez F, F Velasco, JD Carrillo-Ruiz, et al., Comparative evaluation of the effects of unilateral lesion versus electrical stimulation of the globus pallidus internus in advanced Parkinson's disease. *Stereotact Funct Neurosurg,* 2006. **84**(2-3): p. 64-71.
114. Schuurman PR, DA Bosch, PM Bossuyt, et al., A comparison of continuous thalamic stimulation and thalamotomy for suppression of severe tremor. *N Engl J Med,* 2000. **342**(7): p. 461-8.
115. Schuurman PR, J Bruins, MP Merkus, et al., A comparison of neuropsychological effects of thalamotomy and thalamic stimulation. *Neurology,* 2002. **59**(8): p. 1232-9.
116. Tsubokawa T, Y Katatama, Lesion-making surgery versus brain stimulation for treatment of Parkinson's disease. *Critical Reviews in Neurosurgery,* 1999. **9**(2): p. 96-106.
117. Medtronic. *Deep Brain Stimulation for Movement Disorders / Products and Procedures*. 2011; Available from: http://professional.medtronic.com/pt/neuro/dbs-md/prod/index.htm.
118. Loher TJ, HH Capelle, A Kaelin-Lang, et al., Deep brain stimulation for dystonia: outcome at long-term follow-up. *J Neurol,* 2008. **255**(6): p. 881-4.
119. Vidailhet M, L Vercueil, JL Houeto, et al., Bilateral deep-brain stimulation of the globus pallidus in primary generalized dystonia. *N Engl J Med,* 2005. **352**(5): p. 459-67.
120. Kiss ZH, K Doig-Beyaert, M Eliasziw, et al., The Canadian multicentre study of deep brain stimulation for cervical dystonia. *Brain,* 2007. **130**(Pt 11): p. 2879-86.
121. Hung SW, C Hamani, AM Lozano, et al., Long-term outcome of bilateral pallidal deep brain stimulation for primary cervical dystonia. *Neurology,* 2007. **68**(6): p. 457-9.
122. Loher TJ, JM Burgunder, T Pohle, et al., Long-term pallidal deep brain stimulation in patients with advanced Parkinson disease: 1-year follow-up study. *J Neurosurg,* 2002. **96**(5): p. 844-53.
123. Limousin P, P Krack, P Pollak, et al., Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. *N Engl J Med,* 1998. **339**(16): p. 1105-11.
124. Blomstedt P, GM Hariz, MI Hariz, et al., Thalamic deep brain stimulation in the treatment of essential tremor: a long-term follow-up. *Br J Neurosurg,* 2007. **21**(5): p. 504-9.
125. Mundinger F, [Clinical and operative experiences of stereotactic subthalamotomy for involuntary movement disorders]. *Acta 25. Coventus Neuropsychiatrici et EEG Hungarici, Budapestini.,* 1966.
126. Velasco F, F Jimenez, ML Perez, et al., Electrical stimulation of the prelemniscal radiation in the treatment of Parkinson's disease: an old target revised with new techniques. *Neurosurgery,* 2001. **49**(2): p. 293-306.
127. Velasco F, M Velasco, A reticulothalamic system mediating proprioceptive attention and tremor in man. *Neurosurgery,* 1979. **4**(1): p. 30-6.
128. Velasco F, M Velasco, JP Machado, A statisticl outline of the subthalamic target for the arrest of tremor. *Appl Neurophysiol,* 1975. **38**(1): p. 38-46.

129. Velasco F, M Velasco, C Ogarrio, et al., Neglect induced by thalamotomy in humans: a quantitative appraisal of the sensory and motor deficits. *Neurosurgery,* 1986. **19**(5): p. 744-51.
130. Velasco FC, P Molina-Negro, C Bertrand, et al., Further definition of the subthalamic target for arrest of tremor. *J Neurosurg,* 1972. **36**(2): p. 184-91.
131. Hardy J, Historical background of stereotactic surgery: Reflections on stereotactic surgery and the introduction of microelectrode recording in montreal. *Neurosurgery,* 2004. **54**(6): p. 1508-10.
132. Bertrand CM, Surgery of involuntary movements, particularly stereotactic surgery: reminiscences. *Neurosurgery,* 2004. **55**(3): p. 698-703.
133. Bertrand G, J Blundell, R Musella, Electrical exploration of the internal capsule and neighboring structures during stereotactic procedures. *Thirty-first annual meeting of the Harvey Cushing society,* 1963: p. 48.
134. Mundinger F, Stereotaxic interventions on the zona incerta area for treatment of extrapyramidal motor disturbances and their results. *Confin Neurol,* 1965. **26**(3): p. 222-30.
135. Mundinger F, [Subthalamotomy for the treatment of extrapyramidal movement disorders]. *Dtsch Med Wochenschr,* 1965. **90**(45): p. 2002-7.
136. Blacker HM, C Bertrand, N Martinez, et al., Hypotonia accompanying the neurosurgical relief of essential tremor. *J Nerv Ment Dis,* 1968. **147**(1): p. 49-55.
137. Johansson G, L Laitinen, Electrical stimulation of the thalamic and subthalamic area in Parkinson's disease. *Confin Neurol,* 1965. **26**(3): p. 445-50.
138. Johansson GG, LV Laitinen, Threshold stimulation of a human thalamic-subthalamic target area before and after electrocoagulation. *Confin Neurol,* 1970. **32**(2): p. 272-5.
139. Laitinen LV, Stereotaxic Treatment of Hereditary Tremor. *Acta Neurol Scand,* 1965. **41**: p. 74-9.
140. Laitinen LV, Thalamic targets in the stereotaxic treatment of Parkinson's disease. *J Neurosurg,* 1966. **24**(1): p. 82-5.
141. Plaha P, Y Ben-Shlomo, NK Patel, et al., Stimulation of the caudal zona incerta is superior to stimulation of the subthalamic nucleus in improving contralateral parkinsonism. *Brain,* 2006. **129**(Pt 7): p. 1732-47.
142. Morel A**,** Stereotactic Atlas of the Human Thalamus and Basal Ganglia. 2007, New York, NY 10016: Informa Healthcare. 149.
143. Schaltenbrand G, W Wahren**,** Atlas for stereotaxy of the human brain. 2 ed. 1977, Stuttgart: Thieme G.
144. Alvarez L, R Macias, N Pavon, et al., Therapeutic efficacy of unilateral subthalamotomy in Parkinson's disease: results in 89 patients followed for up to 36 months. *J Neurol Neurosurg Psychiatry,* 2009. **80**(9): p. 979-85.
145. Chen CC, ST Lee, T Wu, et al., Hemiballism after subthalamotomy in patients with Parkinson's disease: report of 2 cases. *Mov Disord,* 2002. **17**(6): p. 1367-71.
146. Alvarez L, R Macias, J Guridi, et al., Dorsal subthalamotomy for Parkinson's disease. *Mov Disord,* 2001. **16**(1): p. 72-8.
147. Alvarez L, R Macias, G Lopez, et al., Bilateral subthalamotomy in Parkinson's disease: initial and long-term response. *Brain,* 2005. **128**(Pt 3): p. 570-83.
148. Gill SS, P Heywood, Bilateral dorsolateral subthalamotomy for advanced Parkinson's disease. *Lancet,* 1997. **350**(9086): p. 1224.
149. Patel NK, P Heywood, K O'Sullivan, et al., Unilateral subthalamotomy in the treatment of Parkinson's disease. *Brain,* 2003. **126**(Pt 5): p. 1136-45.

150. Crossman AR, MA SambrookA Jackson, Experimental hemichorea/hemiballismus in the monkey. Studies on the intracerebral site of action in a drug-induced dyskinesia. *Brain,* 1984. **107 (Pt 2)**: p. 579-96.
151. Carpenter MB, Ballism associated with partial destruction of the subthalamic nucleus of luys. *Neurology,* 1955. **5**(7): p. 479-89.
152. Albin RL, The pathophysiology of chorea/ballism and Parkinsonism. *Parkinsonism Relat Disord,* 1995. **1**(1): p. 3-11.
153. Fager CA, Evaluation of thalamic and subthalamic surgical lesions in the alleviation of Parkinson's disease. *J Neurosurg,* 1968. **28**(2): p. 145-9.
154. Guridi JJ, A Obeso, The subthalamic nucleus, hemiballismus and Parkinson's disease: reappraisal of a neurosurgical dogma. *Brain,* 2001. **124**(Pt 1): p. 5-19.
155. Spiegel E, EG Szekely, J Adams, et al., Campotomy in various extrapyramidal disorders. *Thirty-first annual meeting of the Harvey Cushing society,* 1963: p. 46-47.
156. Spiegel EA, HT Wycis**,** Stereoencephalotomy. Part II: Clinical and physiological applications. 1962, New York: Grune & Stratton.
157. Meyers R, WJ Fry, FJ Fry, et al., Early experiences with ultrasonic irradiation of the pallidofugal and nigral complexes in hyperkinetic and hypertonic disorders. *J Neurosurg,* 1959. **16**(1): p. 32-54.
158. Rand RW, Substantia nigralysis. A new surgical technique for treatment of Parkinson's disease and other hyperkinetic syndromes. *Bull Los Angel Neuro Soc,* 1959. **24**: p. 214-6.
159. Blomstedt P, A Fytagoridis, S Tisch, Deep brain stimulation of the posterior subthalamic area in the treatment of tremor. *Acta Neurochir (Wien),* 2009. **151**(1): p. 31-6.
160. Blomstedt P, U Sandvik, S Tisch, Deep brain stimulation in the posterior subthalamic area in the treatment of essential tremor. *Mov Disord,* 2010. **25**(10): p. 1350-6.
161. Andy OJ, MF Jurko, Alteration in Parkinson's tremor during electrode insertion. *Confin Neurol,* 1965. **26**(3): p. 378-81.
162. Hullay J, Subthalamotomy in Parkinson's disease. Analysis of responses to electrostimulation. *Acta Med Acad Sci Hung,* 1971. **28**(1): p. 57-68.
163. Hullay J, J Velok, R Gombi, et al., Subthalamotomy in Parkinson's disease. *Confin Neurol,* 1970. **32**(2): p. 345-8.
164. Jimenez F, F Velasco, M Velasco, et al., Subthalamic prelemniscal radiation stimulation for the treatment of Parkinson's disease: electrophysiological characterization of the area. *Arch Med Res,* 2000. **31**(3): p. 270-81.
165. Kitagawa M, J Murata, H Uesugi, et al., Two-year follow-up of chronic stimulation of the posterior subthalamic white matter for tremor-dominant Parkinson's disease. *Neurosurgery,* 2005. **56**(2): p. 281-9.
166. Krauss JK, M Mohadjer, F Nobbe, et al., The treatment of posttraumatic tremor by stereotactic surgery. Symptomatic and functional outcome in a series of 35 patients. *J Neurosurg,* 1994. **80**(5): p. 810-9.
167. Laitinen LV, Short-term results of stereotaxic treatment for infantile cerebral palsy. *Confin Neurol,* 1965. **26**(3): p. 258-63.
168. Houdart R, H Mamo, M Dondey, et al., [Results of subthalamic coagulations in Parkinson's disease (apropos of 50 cases)]. *Rev Neurol (Paris),* 1965. **112**(6): p. 521-9.
169. Mamo H, M Dondey, J Cophignon, et al., [Transitory latero-pulsion after subthalamic and thalamic coagulations in parkinsonism patients]. *Rev Neurol (Paris),* 1965. **112**(6): p. 509-20.
170. Story JL, LA French, SN Chou, et al., Experiences with subthalamic lesions in patients with movement disorders. *Confin Neurol,* 1965. **26**(3): p. 218-21.

171. Mundinger F, C Ostertag, Multilocular lesions in the therapy of cerebral palsy. *Acta Neurochir (Wien),* 1977(Suppl 24): p. 11-4.
172. Kandel EI, A Guluev Kh, [Treatment of hemihyperkinesis by stereotaxic surgery on the basal ganglia]. *Zh Vopr Neirokhir Im N N Burdenko,* 1977(6): p. 29-33.
173. Kandel EI, [Stereotaxic method of treating extrapyramidal spastic torticollis]. *Zh Vopr Neirokhir Im N N Burdenko,* 1984(6): p. 28-34.
174. Riechert T, D Richter, [Stereotaxic operations in the treatment of the tremors in multiple sclerosis]. *Schweiz Arch Neurol Neurochir Psychiatr,* 1972. **111**(2): p. 411-6.
175. Mundinger F, T Riechert, J Disselhoff, Long term results of stereotaxic operations on extrapyramidal hyperkinesia (excluding parkinsonism). *Confin Neurol,* 1970. **32**(2): p. 71-8.
176. Krauss JK, F Mundinger, Functional stereotactic surgery for hemiballism. *J Neurosurg,* 1996. **85**(2): p. 278-86.
177. Houdart R, J Cophignon, M Dondey, [Comparison of the effects of limited thalamic and sub-thalamic stereotaxic lesions]. *Confin Neurol,* 1966. **27**(1): p. 246-50.
178. Hughes B, Evaluation of the subthalamic lesion in parkinsonism, in Third symposium on Parkinson's diease, Gillingham FJ and Donaldson IML, Editors. 1969, Livingstone, E.S.: Edinburgh. p. 259-60.
179. Ito Z, Stimulation and destruction of the prelemniscal radiation or its adjacent area in various extrapyramidal disorders. *Confin Neurol,* 1975. **37**(1-3): p. 41-8.
180. Lücking CH, *[The importance of the subthalamic structures in the stereotactic operations for tremor]*, in *Munich*. 1973, Munich.
181. Narabayashi H, K Kubota, Reconsideration of ventrolateral thalamotomy for hyperkinesis. *Prog Brain Res,* 1966. **21**: p. 339-49.
182. Mohadjer M, H Goerke, E Milios, et al., Long-term results of stereotaxy in the treatment of essential tremor. *Stereotact Funct Neurosurg,* 1990. **54-55**: p. 125-9.
183. Riechert T, D Richter, [Surgical treatment of multiple sclerosis tremor and essential tremor]. *Munch Med Wochenschr,* 1972. **114**(46): p. 2025-8.
184. Arsalo A, A Hanninen, L Laitinen, Functional neurosurgery in the treatment of multiple sclerosis. *Ann Clin Res,* 1973. **5**(2): p. 74-9.
185. Mundinger F, T Riechert, J Disselhoff, Long-term results of stereotactic treatment of spasmodic torticollis. *Confin Neurol,* 1972. **34**(2): p. 41-50.
186. Riechert T, The stereotactic technique and its application in extrapyramidal hyperkinesia. *Confin Neurol,* 1972. **34**(5): p. 325-30.
187. Nittner K, The combined thalamo-subthalamotomy. *Confin Neurol,* 1970. **32**(2): p. 93-9.
188. Nittner K, Hypokinetic syndromes and their therapy. *Confin Neurol,* 1972. **34**(2): p. 55-6.
189. Mundinger F, T Riechert, [Indication and long-term results with 1400 uni- and bilateral stereotaxic operations in Parkinson's syndrome]. *Wien Z Nervenheilkd Grenzgeb,* 1966. **23**(1): p. 147-77.
190. Johansson GG, Electrical stimulation of a human ventrolateral-subventrolateral thalamic target area. I. The stimulation method and the application of repeated stimulus trains of constant composition. *Acta Physiol Scand,* 1969. **75**(3): p. 433-45.
191. Johansson GG, Electrical stimulation of a human ventrolateral-subventrolateral thalamic target area. II. Combination of different durations of single pulses with the peak current just adequate to evoke clinical responses. *Acta Physiol Scand,* 1969. **75**(3): p. 446-55.
192. Johansson GG, Electrical stimulation of a human ventrolateral-subventrolateral thalamic target area. III. Combination of different pulse repetition frequencies with the

peak current just adequate to evoke clinical responses. *Acta Physiol Scand,* 1969. **75**(3): p. 456-67.
193. Johansson GG, Electrical stimulation of a human ventrolateral-subventrolateral thalamic target area. IV. Combination of different pulse repetition frequencies with the pulse duration just adequate to evoke clinical responses. *Acta Physiol Scand,* 1969. **75**(3): p. 468-75.
194. Bergstrom MR, GG Johansson, LV Laitinen, et al., Electrical stimulation of the thalamic and subthalamic area in cerebral palsy. *Acta Physiol Scand,* 1966. **67**(2): p. 208-13.
196. Kitagawa M, J Murata, S Kikuchi, et al., Deep brain stimulation of subthalamic area for severe proximal tremor. *Neurology,* 2000. **55**(1): p. 114-6.
197. Murata J, M Kitagawa, H Uesugi, et al., Electrical stimulation of the posterior subthalamic area for the treatment of intractable proximal tremor. *J Neurosurg,* 2003. **99**(4): p. 708-15.
198. Hirai T, M Miyazaki, H Nakajima, et al., The correlation between tremor characteristics and the predicted volume of effective lesions in stereotaxic nucleus ventralis intermedius thalamotomy. *Brain,* 1983. **106**: p. 1001-18.
199. Yasui N, H Narabayashi, T Kondo, et al., Slight cerebellar signs in stereotactic thalamotomy and subthalamotomy for parkinsonism. *Appl Neurophysiol,* 1976. **39**(3-4): p. 315-20.
200. Struppler A, D Burg, CH Lucking, et al., The mode of innervation following thalamotomy and subthalamotomy. *Confin Neurol,* 1974. **36**(4-6): p. 347-54.
201. Vilkki J, Visual hemi-inattention after ventrolateral thalamotomy. *Neuropsychologia,* 1984. **22**(4): p. 399-408.
202. Zager EL, Neurosurgical management of spasticity, rigidity, and tremor. *Neurol Clin,* 1987. **5**(4): p. 631-47.
203. Schiffter R, P Pohl, [Course of the descending central sympathetic pathway. Results of sweat secretion tests following stereotaxic subthalamotomy]. *Arch Psychiatr Nervenkr,* 1972. **216**(4): p. 379-92.
204. Kim YK, HP Buscher, [Control of autonomic tonus in stereotaxic subthalamotomy]. *Neurochirurgia (Stuttg),* 1970. **13**(5): p. 151-64.
205. Kim YK, W Umbach, The effects of stereotaxic subthalamotomy on sympathetic tonus. *Confin Neurol,* 1972. **34**(2): p. 156-61.
206. Selby GS, Parkinson's disease, in Diseases of basal ganglia, Vinken PJ and Bruyn WG, Editors. 1969. p. 173-207.
207. Ojemann GA, KB Hoyenga, AA Ward, Jr., Prediction of short-term verbal memory disturbance after ventrolateral thalamotomy. *J Neurosurg,* 1971. **35**(2): p. 203-10.
208. Ojemann GA, AA Ward, Jr., Present indications for L-dopa and thalamotomy in the treatment of Parkinson's disease. *Northwest Med,* 1971. **70**(2): p. 101-4.
209. Ojemann GA, AA Ward, Jr., Speech representation in ventrolateral thalamus. *Brain,* 1971. **94**(4): p. 669-80.
210. Hugdahl K, K Wester, A Asbjornsen, The role of the left and right thalamus in language asymmetry: dichotic listening in Parkinson patients undergoing stereotactic thalamotomy. *Brain Lang,* 1990. **39**(1): p. 1-13.
211. Bell DS, Speech functions of the thalamus inferred from the effects of thalamotomy. *Brain,* 1968. **91**(4): p. 619-38.
212. Samra K, M Riklan, E Levita, et al., Language and speech correlates of anatomically verified lesions in thalamic surgery for parkinsonism. *J Speech Hear Res,* 1969. **12**(3): p. 510-40.

213. Vilkki J, Effects of thalamic lesions on complex perception and memory. *Neuropsychologia,* 1978. **16**(4): p. 427-37.
214. Vilkki J, LV Laitinen, Effects of pulvinotomy and ventrolateral thalamotomy on some cognitive functions. *Neuropsychologia,* 1976. **14**(1): p. 67-78.
215. Blomstedt P, MI Hariz, Deep brain stimulation for movement disorders before DBS for movement disorders. *Parkinsonism Relat Disord,* 2010. **16**(7): p. 429-33.
216. Hariz MI, P Blomstedt, L Zrinzo, Deep brain stimulation between 1947 and 1987: the untold story. *Neurosurg Focus,* 2010. **29**(2): p. E1.
217. Mundinger F, [New stereotactic treatment of spasmodic torticollis with a brain stimulation system]. *Med Klin,* 1977. **72**(46): p. 1982-6.
218. Brice J, L McLellan, Suppression of intention tremor by contingent deep-brain stimulation. *Lancet,* 1980. **1**(8180): p. 1221-2.
219. Andy OJ, Thalamic stimulation for control of movement disorders. *Appl Neurophysiol,* 1983. **46**(1-4): p. 107-11.
220. Plaha P, S Javed, D Agombar, et al., Bilateral caudal zona incerta nucleus stimulation for essential tremor: outcome and quality of life. *J Neurol Neurosurg Psychiatry,* 2011. **82**(8): p. 899-904.
221. Plaha P, S Khan, SS Gill, Bilateral stimulation of the caudal zona incerta nucleus for tremor control. *J Neurol Neurosurg Psychiatry,* 2008. **79**(5): p. 504-13.
222. Plaha P, NK Patel, SS Gill, Stimulation of the subthalamic region for essential tremor. *J Neurosurg,* 2004. **101**(1): p. 48-54.
223. Freund HJ, UB Barnikol, D Nolte, et al., Subthalamic-thalamic DBS in a case with spinocerebellar ataxia type 2 and severe tremor-A unusual clinical benefit. *Mov Disord,* 2007. **22**(5): p. 732-5.
224. Fytagoridis A, U Sandvik, M Astrom, et al., Long term follow-up of deep brain stimulation of the caudal zona incerta for essential tremor. *J Neurol Neurosurg Psychiatry,* 2011.
225. Carrillo-Ruiz JD, F Velasco, F Jimenez, et al., Bilateral Electrical Stimulation of Prelemniscal Radiations in the Treatment of Advanced Parkinson's Disease. *Neurosurgery,* 2008. **62**: p. 347-59.
226. Carrillo-Ruiz JD, F Velasco, F Jimenez, et al., Neuromodulation of prelemniscal radiations in the treatment of Parkinson's disease. *Acta Neurochir Suppl,* 2007. **97**(Pt 2): p. 185-90.
227. Khan S, L Mooney, P Plaha, et al., Outcomes from stimulation of the caudal zona incerta and pedunculopontine nucleus in patients with Parkinson's disease. *Br J Neurosurg,* 2011.
228. Hooper J, P Simpson, IR Whittle, Chronic posttraumatic movement disorder alleviated by insertion of meso-diencephalic deep brain stimulating electrode. *Br J Neurosurg,* 2001. **15**(5): p. 435-8.
229. Blomstedt P, U Sandvik, MI Hariz, et al., Influence of age, gender and severity of tremor on outcome after thalamic and subthalamic DBS for essential tremor. *Parkinsonism Relat Disord,* 2011. **17**(8): p. 617-20.
230. Blomstedt P, U Sandvik, J Linder, et al., Deep brain stimulation of the subthalamic nucleus versus the zona incerta in the treatment of essential tremor. *Acta Neurochir (Wien),* 2011. **153**(12): p. 2329-35.
231. Herzog J, U Fietzek, W Hamel, et al., Most effective stimulation site in subthalamic deep brain stimulation for Parkinson's disease. *Mov Disord,* 2004. **19**(9): p. 1050-4.
232. Pollo C, F Vingerhoets, E Pralong, et al., Localization of electrodes in the subthalamic nucleus on magnetic resonance imaging. *J Neurosurg,* 2007. **106**(1): p. 36-44.

233. Saint-Cyr JA, T Hoque, LC Pereira, et al., Localization of clinically effective stimulating electrodes in the human subthalamic nucleus on magnetic resonance imaging. *J Neurosurg,* 2002. **97**(5): p. 1152-66.
234. Fytagoridis A, P Blomstedt, Complications and side effects of deep brain stimulation in the posterior subthalamic area. *Stereotact Funct Neurosurg,* 2010. **88**(2): p. 88-93.
235. Parent M, A Parent, The pallidofugal motor fiber system in primates. *Parkinsonism Relat Disord,* 2004. **10**(4): p. 203-11.
236. Barbe MT, L Liebhart, M Runge, et al., Deep brain stimulation of the ventral intermediate nucleus in patients with essential tremor: Stimulation below intercommissural line is more efficient but equally effective as stimulation above. *Exp Neurol,* 2011.
237. Hamel W, J Herzog, F Kopper, et al., Deep brain stimulation in the subthalamic area is more effective than ventralis intermedius stimulation for bilateral intention tremor. *Acta neurochirurgica,* 2007. **149**(8): p. 749-58.
238. Papavassiliou E, G Rau, S Heath, et al., Thalamic deep brain stimulation for essential tremor: relation of lead location to outcome. *Neurosurgery,* 2004. **54**(5): p. 1120-29.
239. Mobin F, A, A De Salles, EJ Behnke, et al., Correlation between MRI-based stereotactic thalamic deep brain stimulation electrode placement, macroelectrode stimulation and clinical response to tremor control. *Stereotact Funct Neurosurg,* 1999. **72**(2-4): p. 225-32.
240. Herzog J, W Hamel, R Wenzelburger, et al., Kinematic analysis of thalamic versus subthalamic neurostimulation in postural and intention tremor. *Brain,* 2007. **130**(Pt 6): p. 1608-25.
241. Sandvik U, Koskinen LO, et al., Thalamic and Subthalamic DBS for Essential Tremor: Where Is the Optimal Target? *Neurosurgery,* 2011.
242. Forel A, Untersuchungen über die Haubenregion und ihre oberen Verknüpfungen im Gehirne des Menschen und einiger Säugethiere, mit Beiträgen zu den Methoden der Gehirnuntersuchung. , in Archiv für Psychiatrie und Nervenkrankheiten 1877. p. 393-495.
243. Mitrofanis J, Some certainty for the "zone of uncertainty"? Exploring the function of the zona incerta. *Neuroscience,* 2005. **130**(1): p. 1-15.
244. Mitrofanis J, K Ashkan, BA Wallace, et al., Chemoarchitectonic heterogeneities in the primate zona incerta: clinical and functional implications. *J Neurocytol,* 2004. **33**(4): p. 429-40.
245. Romanowski CA, IJ Mitchell, AR Crossman, The organisation of the efferent projections of the zona incerta. *J Anat,* 1985. **143**: p. 75-95.
246. Roger M, J Cadusseau, Afferents to the zona incerta in the rat: a combined retrograde and anterograde study. *J Comp Neurol,* 1985. **241**(4): p. 480-92.
247. May PJ, W Sun, WC Hall, Reciprocal connections between the zona incerta and the pretectum and superior colliculus of the cat. *Neuroscience,* 1997. **77**(4): p. 1091-114.
248. Bartho P, TF Freund, L Acsady, Selective GABAergic innervation of thalamic nuclei from zona incerta. *Eur J Neurosci,* 2002. **16**(6): p. 999-1014.
249. Bartho P, A Slezia, V Varga, et al., Cortical control of zona incerta. *J Neurosci,* 2007. **27**(7): p. 1670-81.
250. Kolmac CJ Mitrofanis, Organization of the basal forebrain projection to the thalamus in rats. *Neurosci Lett,* 1999. **272**(3): p. 151-4.
251. Kolmac CI, BD Power, J Mitrofanis, Patterns of connections between zona incerta and brainstem in rats. *J Comp Neurol,* 1998. **396**(4): p. 544-55.
252. Power BD, CI Kolmac, J Mitrofanis, Evidence for a large projection from the zona incerta to the dorsal thalamus. *J Comp Neurol,* 1999. **404**(4): p. 554-65.

253. Lin CS, MA Nicolelis, JS Schneider, et al., A major direct GABAergic pathway from zona incerta to neocortex. *Science,* 1990. **248**(4962): p. 1553-6.
254. Heise CE, J Mitrofanis, Evidence for a glutamatergic projection from the zona incerta to the basal ganglia of rats. *J Comp Neurol,* 2004. **468**(4): p. 482-95.
255. Lavallee P, N Urbain, C Dufresne, et al., Feedforward inhibitory control of sensory information in higher-order thalamic nuclei. *J Neurosci,* 2005. **25**(33): p. 7489-98.
256. Nicolelis MA, JK Chapin, RC Lin, Somatotopic maps within the zona incerta relay parallel GABAergic somatosensory pathways to the neocortex, superior colliculus, and brainstem. *Brain Res,* 1992. **577**(1): p. 134-41.
257. Trageser JC, KA Burke, R Masri, et al., State-dependent gating of sensory inputs by zona incerta. *J Neurophysiol,* 2006. **96**(3): p. 1456-63.
258. Trageser JC, A Keller, Reducing the uncertainty: gating of peripheral inputs by zona incerta. *J Neurosci,* 2004. **24**(40): p. 8911-5.
259. Benazzouz A, S Breit, A Koudsie, et al., Intraoperative microrecordings of the subthalamic nucleus in Parkinson's disease. *Mov Disord,* 2002. **17 Suppl 3**: p. S145-9.
260. Merello M, E Tenca, D Cerquetti, Neuronal activity of the zona incerta in Parkinson's disease patients. *Mov Disord,* 2006. **21**(7): p. 937-43.
261. Gallay MN, D Jeanmonod, J Liu, et al., Human pallidothalamic and cerebellothalamic tracts: anatomical basis for functional stereotactic neurosurgery. *Brain Struct Funct,* 2008. **212**(6): p. 443-63.
262. Velasco M, F Velasco, Differential effect of task relevance on early and late components of cortical and subcortical somatic evoked potentials in man. *Electroencephalogr Clin Neurophysiol,* 1975. **39**(4): p. 353-64.
263. Krack P, J Dostrovsky, I Ilinsky, et al., Surgery of the motor thalamus: problems with the present nomenclatures. *Mov Disord,* 2002. **17 Suppl 3**: p. S2-8.
264. Ilinsky I, K Kultas-Ilinsky, Motor thalamic circuits in primates with emphasis on the area targeted in treatment of movement disorders. *Mov Disord,* 2002. **17 Suppl 3**: p. S9-14.
265. Deuschl G, P Bain, M Brin, Consensus statement of the Movement Disorder Society on Tremor. Ad Hoc Scientific Committee. *Mov Disord,* 1998. **13 Suppl 3**: p. 2-23.
266. Elble R, G Deuschl, Milestones in tremor research. *Mov Disord,* 2011. **26**(6): p. 1096-105.
267. Deuschl G, H Bergman, Pathophysiology of nonparkinsonian tremors. *Mov Disord,* 2002. **17 Suppl 3**: p. S41-8.
268. Raethjen J, M Lindemann, H Schmaljohann, et al., Multiple oscillators are causing parkinsonian and essential tremor. *Mov Disord,* 2000. **15**(1): p. 84-94.
269. Timmermann L, J Gross, M Dirks, et al., The cerebral oscillatory network of parkinsonian resting tremor. *Brain,* 2003. **126**(Pt 1): p. 199-212.
270. Halliday DM, BA Conway, SF Farmer, et al., Coherence between low-frequency activation of the motor cortex and tremor in patients with essential tremor. *Lancet,* 2000. **355**(9210): p. 1149-53.
271. Hellwig B, S Haussler, B Schelter, et al., Tremor-correlated cortical activity in essential tremor. *Lancet,* 2001. **357**(9255): p. 519-23.
272. McIntyre CC, S Mori, DL Sherman, et al., Electric field and stimulating influence generated by deep brain stimulation of the subthalamic nucleus. *Clin Neurophysiol,* 2004. **115**(3): p. 589-95.
273. McIntyre CC, M Savasta, L Kerkerian-Le Goff, et al., Uncovering the mechanism(s) of action of deep brain stimulation: activation, inhibition, or both. *Clin Neurophysiol,* 2004. **115**(6): p. 1239-48.

274. McIntyre CC, M Savasta, BL Walter, et al., How does deep brain stimulation work? Present understanding and future questions. *J Clin Neurophysiol,* 2004. **21**(1): p. 40-50.
275. McIntyre CC, NV Thakor, Uncovering the mechanisms of deep brain stimulation for Parkinson's disease through functional imaging, neural recording, and neural modeling. *Crit Rev Biomed Eng,* 2002. **30**(4-6): p. 249-81.
276. Johnson MD, S Miocinovic, CC McIntyre, et al., Mechanisms and targets of deep brain stimulation in movement disorders. *Neurotherapeutics,* 2008. **5**(2): p. 294-308.
277. Hammond C, R Ammari, B Bioulac, et al., Latest view on the mechanism of action of deep brain stimulation. *Mov Disord,* 2008. **23**(15): p. 2111-21.
278. Pollak P, P Krack, V Fraix, et al., Intraoperative micro- and macrostimulation of the subthalamic nucleus in Parkinson's disease. *Mov Disord,* 2002. **17 Suppl 3**: p. S155-61.
279. Tommasi G, P Krack, V Fraix, et al., Pyramidal tract side effects induced by deep brain stimulation of the subthalamic nucleus. *J Neurol Neurosurg Psychiatry,* 2008. **79**(7): p. 813-9.
280. Parsons TD, SA Rogers, AJ Braaten, et al., Cognitive sequelae of subthalamic nucleus deep brain stimulation in Parkinson's disease: a meta-analysis. *Lancet Neurol,* 2006. **5**(7): p. 578-88.
281. Fields JA, AI Troster, SP Woods, et al., Neuropsychological and quality of life outcomes 12 months after unilateral thalamic stimulation for essential tremor. *J Neurol Neurosurg Psychiatry,* 2003. **74**(3): p. 305-11.
282. Witt K, C Daniels, J Reiff, et al., Neuropsychological and psychiatric changes after deep brain stimulation for Parkinson's disease: a randomised, multicentre study. *Lancet Neurol,* 2008. **7**(7): p. 605-14.
283. Flora ED, CL Perera, AL Cameron, et al., Deep brain stimulation for essential tremor: a systematic review. *Mov Disord,* 2010. **25**(11): p. 1550-9.
284. Deuschl G, J Raethjen, H Hellriegel, et al., Treatment of patients with essential tremor. *Lancet Neurol,* 2011. **10**(2): p. 148-61.
285. Lyons K, R Pahwa, C Comella, et al., Benefits and risks of pharmacological treatments for essential tremor. *Drug Saf,* 2003. **26**(7): p. 461-81.
286. Weaver FM, K Follett, M Stern, et al., Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. *Jama,* 2009. **301**(1): p. 63-73.
287. Hughes AJ, SE Daniel, L Kilford, et al., Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry,* 1992. **55**(3): p. 181-4.
288. Fahn S, E Tolosa, C Marin, Clinical rating scale for tremor, in Parkinson´s disease and movementdisorders, Jankovic J and Tolosa E, Editors. 1993, Urban and Schwarzenberg: Munich. p. 271-80.
289. Volkmann J, C Daniels, K Witt, Neuropsychiatric effects of subthalamic neurostimulation in Parkinson disease. *Nat Rev Neurol,* 2010. **6**(9): p. 487-98.
290. Crinion J, R Turner, A Grogan, et al., Language control in the bilingual brain. *Science,* 2006. **312**(5779): p. 1537-40.
291. Bhatnagar S, H Buckingham, Neurogenic stuttering: its reticular modulation. *Curr Neurol Neurosci Rep,* 2010. **10**(6): p. 491-8.
292. Selby G, Stereotactic surgery for the relief of Parkinson's disease. 2. An analysis of the results in a series of 303 patients (413 operations). *J Neurol Sci,* 1967. **5**(2): p. 343-75.

293. Johnson MD, GA Ojemann, The role of the human thalamus in language and memory: evidence from electrophysiological studies. *Brain Cogn,* 2000. **42**(2): p. 218-30.
294. Vilkki J, LV Laitinen, Differential effects of left and right ventrolateral thalamotomy on receptive and expressive verbal performances and face-matching. *Neuropsychologia,* 1974. **12**(1): p. 11-9.
295. Ojemann GA, Alteration in nonverbal short term memory with stimulation in the region of the mammillothalamic tract in man. *Neuropsychologia,* 1971. **9**(2): p. 195-201.
296. Ashkan K, P Blomstedt, L Zrinzo, et al., Variability of the subthalamic nucleus: the case for direct MRI guided targeting. *Br J Neurosurg,* 2007. **21**(2): p. 197-200.
297. Hirabayashi H, M Tengvar, MI Hariz, Stereotactic imaging of the pallidal target. *Mov Disord,* 2002. **17**: p. S130-4.
298. Deuschl G, J Herzog, G Kleiner-Fisman, et al., Deep brain stimulation: postoperative issues. *Mov Disord,* 2006. **21 Suppl 14**: p. S219-37.
299. Klostermann F, F Ehlen, J Vesper, et al., Effects of subthalamic deep brain stimulation on dysarthrophonia in Parkinson's disease. *J Neurol Neurosurg Psychiatry,* 2008. **79**(5): p. 522-9.
300. Pinto S, M Gentil, P Krack, et al., Changes induced by levodopa and subthalamic nucleus stimulation on parkinsonian speech. *Mov Disord,* 2005. **20**(11): p. 1507-15.
301. Astrom M, LU Zrinzo, S Tisch, et al., Method for patient-specific finite element modeling and simulation of deep brain stimulation. *Med Biol Eng Comput,* 2009. **47**(1): p. 21-8.
302. Astrom M, E Tripoliti, MI Hariz, et al., Patient-specific model-based investigation of speech intelligibility and movement during deep brain stimulation. *Stereotact Funct Neurosurg,* 2010. **88**(4): p. 224-33.
303. Tripoliti E, L Zrinzo, I Martinez-Torres, et al., Effects of subthalamic stimulation on speech of consecutive patients with Parkinson disease. *Neurology,* 2011. **76**(1): p. 80-6.
304. Diamond A, C Kenney, M Almaguer, et al., Hyperhidrosis due to deep brain stimulation in a patient with essential tremor. Case report. *J Neurosurg,* 2007. **107**(5): p. 1036-8.
305. Pahwa R, KE Lyons, SB Wilkinson, et al., Long-term evaluation of deep brain stimulation of the thalamus. *J Neurosurg,* 2006. **104**(4): p. 506-12.
306. Koller WC, KE Lyons, SB Wilkinson, et al., Long-term safety and efficacy of unilateral deep brain stimulation of the thalamus in essential tremor. *Mov Disord,* 2001. **16**(3): p. 464-8.
307. Zhang K, S Bhatia, MY Oh, et al., Long-term results of thalamic deep brain stimulation for essential tremor. *J Neurosurg,* 2010. **112**(6): p. 1271-6.
308. Benabid AL, P Pollak, D Gao, et al., Chronic electrical stimulation of the ventralis intermedius nucleus of the thalamus as a treatment of movement disorders. *J Neurosurg,* 1996. **84**(2): p. 203-14.
309. Pilitsis JG, LV Metman, JR Toleikis, et al., Factors involved in long-term efficacy of deep brain stimulation of the thalamus for essential tremor. *J Neurosurg,* 2008. **109**(4): p. 640-6.
310. Hariz MI, P Shamsgovara, F Johansson, et al., Tolerance and tremor rebound following long-term chronic thalamic stimulation for Parkinsonian and essential tremor. *Stereotact Funct Neurosurg,* 1999. **72**(2-4): p. 208-18.
311. Barbe MT, L Liebhart, M Runge, et al., Deep brain stimulation in the nucleus ventralis intermedius in patients with essential tremor: habituation of tremor suppression. *J Neurol,* 2011. **258**(3): p. 434-9.

312. Krack P, A Benazzouz, P Pollak, et al., Treatment of tremor in Parkinson's disease by subthalamic nucleus stimulation. *Mov Disord,* 1998. **13**(6): p. 907-14.
313. Kim HJ, BS Jeon, SH Paek, et al., Bilateral subthalamic deep brain stimulation in Parkinson disease patients with severe tremor. *Neurosurgery,* 2010. **67**(3): p. 626-32; discussion 32.
314. Kumar R, AM Lozano, E Sime, et al., Comparative effects of unilateral and bilateral subthalamic nucleus deep brain stimulation. *Neurology,* 1999. **53**(3): p. 561-6.
315. Slowinski JL, JD Putzke, RJ Uitti, et al., Unilateral deep brain stimulation of the subthalamic nucleus for Parkinson disease. *J Neurosurg,* 2007. **106**(4): p. 626-32.