Stereotactic Functional Procedures
in the Treatment of Essential Tremor

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“I feel my heart glow with an enthusiasm which elevates me to heaven, for nothing contributes so much to tranquilize the mind as a steady purpose - a point on which the soul may fix its intellectual eye”

Mary Wollstonecraft Shelley, Frankenstein, 1818
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Abstract

**Background:** Essential tremor (ET) is the most common movement disorder. In cases resistant to pharmacological treatment, functional stereotactic neurosurgery can be an alternative. Lesional surgery has largely been replaced by deep brain stimulation (DBS). The current target of choice is the ventrolateral thalamus (Vim). Vim DBS has generally shown good results, but in some cases it is associated with a suboptimal effect as well as side effects. DBS in the posterior subthalamic area/caudal zona incerta (PSA/cZi) has recently shown promising effects. Recently the role of lesional therapy in selected cases has been discussed.

**Aim:** The aim is to evaluate stereotactic functional procedures in the treatment of ET, with special emphasis on PSA DBS. Further the effects of DBS in the PSA are evaluated. The optimal target is also assessed by evaluating the effect of Vim and PSA DBS in relation to the position of the electrode. An attempt to identify patient-specific factors of prognostic importance for the outcome after DBS will be made. The quality of life (QoL) of patients treated with PSA DBS for ET will be assessed. Finally, the aim is also to analyze retrospectively the long-term outcome of lesional procedures (thalamotomies).

**Method:** The thesis consists of five studies. The optimal electrode location is evaluated in a study analyzing the location of the electrode contact yielding the best effect in Vim DBS and PSA DBS groups. The efficacy of PSA DBS in 21 patients is evaluated in a prospective study. The correlation between outcome, age, tremor grade and gender is established in a prospective study consisting of 68 patients. Finally, the degree of improvement in QoL is determined in 16 patients operated on in the PSA. The very long-term effect of lesional surgery has been investigated in a retrospective study of nine patients who have undergone thalamotomy.

**Results:** In the study of PSA DBS the total score on the Essential Tremor Rating Scale (ETRS) was reduced by 60% compared to the baseline value. Tremor of the arm was improved by 95%. The study evaluating the optimal contact location showed that the best effect was in the PSA in 54% and in the Vim in 12%. The efficacy of DBS was not related to age, gender, or the severity of tremor with regard to the percentage reduction of tremor on stimulation. In patients with a more severe tremor at baseline, a higher degree of residual tremor on stimulation was seen. With regard to QoL, the activities of daily living (ADL) according to the ETRS score were significantly improved, as well as according to the ADL and psychosocial subscores on the Questionnaire for Essential Tremor (QUEST) scale. No significant changes were found on the generic Short Form (SF-36) QoL scale. Thalamotomy had some positive effects, but also a significant amount of side effects that might be attributed to the surgery.
Conclusions: The effect of PSA DBS was very satisfying and compares well with the results from Vim DBS. When both Vim and PSA DBS are considered, the optimal target seems to be located in the PSA. PSA DBS shows good results in improving ADL, but the results have been difficult to demonstrate on QoL scales. The efficacy of DBS could not be shown to be associated with gender or age. Nor was it associated with the severity of tremor regarding the percentage of tremor reduction on stimulation. The preoperative severity of tremor was the most important factor regarding outcome following DBS. With regard to thalamotomies, some possible remaining benefit of the surgery could be seen along with some severe side effects.

Keywords: Deep brain stimulation, Essential tremor, Thalamotomy, Zona incerta, Posterior subthalamic area, caudal Zona incerta, Quality of Life, Vim
Abbreviations

The following abbreviations are used in the text, the *cursive* ones are abbreviations used only in the Schaltenbrand Atlas.¹

ADL, activities of daily living
AC, anterior commissure
BBS, Berg’s Balance Score
BP, bodily pain, subscore SF-36
CT, computed tomography
Cpip, internal capsule posterior limb
cZi, caudal zona incerta
DBS, deep brain stimulation
ET, essential tremor
ETRS, Essential Tremor Rating Scale
GABA, gamma amionbutyric acid
GH, general health, subscore SF-36
Gpe, globus pallidus externus
Gpi, globus pallidus internus
H, field H of Forel
H1, field H1 of Forel
H2, field H2 of Forel
Hz, hertz
IC, internal capsule
ICL, intercommissural line
IPG, implantable pulse-generator
LINGO1, leucine rich repeat and Ig domain containing 1
LI, lateral lemniscus
Lm, medial lemniscus
MCP, midcommissural point
MCS, Mental Component Score in SF-36
MDS, Movement Disorder Society
MH, mental health, subscore SF-36
Ml, medial lemniscus, *in this thesis referred to as Lm*
MRI, magnetic resonance imaging
MS, multiple sclerosis
Ni, substantia nigra *in this thesis referred to as SN*
PC, posterior commissure
PCS, Physical Component Score in SF-36
PEV, pulse effective voltage
PD, Parkinson’s disease
PF, physical functioning, subscore SF-36
Ppd, pedunculopontine nucleus
PPS, pulses per second
PSA, posterior subthalamic area
PW, pulse-width
Psip, pes lemnisci profundus
Q, fasciculus Q
QUEST, questionnaire in essential tremor, QoL scoring
QUEST-SI, QUEST Summary Index
QoL, quality of life
Raprl, prelemniscal radiation
RE, role emotional, subscore SF-36
RF, role physical, subscore SF-36
Rt, reticular nucleus of thalamus
Ru, nucleus ruber, red nucleus
SF, social functioning, subscore SF-36
SF-36, Short Form-36
5th, nucleus subthalamicus in this thesis referred to as STN
STN, nucleus subthalamicus
SN, substantia nigra
SNC, substantia nigra pars compacta
SNr, substantia nigra pars reticulata
TRIG, Tremor Investigation Group
U, voltage
V, volts
Vc, ventrocaudal nucleus
VcPc, ventrocaudal parvo cellular nucleus
Vim, nucleus ventralis intermedium thalami
Vim.e, external Vim
Vim.i, internal Vim
Voa, ventrooralis anterior nucleus of the thalamus
Vop, ventrooralis posterior nucleus of the thalamus
VT, vitality, subscore SF-36
X, coordinate for laterality
Y, coordinate for antero-posterior direction
Z, coordinate for dorso-ventral direction
Zi, zona incerta
µs, micro-second
Manuscripts

I. Thalamotomy for essential tremor – A Very Long-term Follow-up
Sandvik U, Rosendal Å, van Doorn J, Birgander R, Blomstedt P
Manuscript, submitted for publication

II. Thalamic/Subthalamic DBS for Essential Tremor. What is the Optimal Location of the Electrode?
Sandvik U, Koskinen LO, Lundquist A, Blomstedt P
Neurosurgery, E-published September 2011

III. Deep Brain Stimulation in the Posterior Subthalamic Area in the Treatment of Essential Tremor
Blomstedt P, Sandvik U, Tisch S.
Movement Disorder Journal, 2010 vol 30;25:1350-6

IV. Influence of Age, Gender and Severity of Tremor on Outcome after Thalamic and Subthalamic DBS for Essential Tremor
Parkinsonism and Related Disorders, 2011 vol 11;617-620

V. Effect of PSA DBS on Quality of Life in Essential Tremor
Sandvik U, Hariz GM, Blomstedt P
Manuscript, submitted for publication

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Essentiell tremor (ET) är en av de mest vanliga rörelsestörningarna och bara ungefär hälften av de drabbade är behjälpta av mediciner. Hos vissa individer blir tremorn (skakningar) så uttalad att den kommer att inskränka funktionsförmågan och påverka livskvaliteten på ett menligt vis. Hos patienter med mycket handikappande symptom kan behandling med stereotaktisk funktionell neurokirurgi vara ett alternativ.

Stereotaktisk funktionell kirurgi innebär att man genom att tillämpa en geometrisk modell kan bygga ett tredimensionellt koordinatssystem för att nå svårtillgängliga områden djupt i hjärnan. Den mest vanliga behandlingen är djup hjärnstimulering, deep brain stimulation (DBS), som innebär att man implantar en elektroda i hjärnan och kopplar denna vidare till en batteridosa som placeras under huden, nedom nyckelbenet. DBS i ventrolaterala thalamus (Vim) anses numera vara en standardbehandling för ET.

Eftersom DBS är en dyr behandling med infektionsrisk, upprepade batteribyte och livslång uppföljning har det förekommit diskussioner huruvida en lesionersbehandling (koagulation av områden i hjärnan) skulle kunna vara ett alternativ hos visa patienter. Nio patienter som befanns vara lämpliga för studien följdes upp med avseende på tremor, bieffekter och radiologisk bild. Ingen av patienterna hade fått en bestående positiv effekt, i det bästa fallet hade skakningarna upphört under en tidsperiod på 20 år. I det sämsta fallet hade patienten endast upplevt biverkningar.

Det andra delarbetet handlar om den optimala målområdet för DBS vid ET. På vår klinik används kaudala zona incerta (cZi) som mål. Delarbetet jämför två grupper (Vim och cZi) och visar på att den bästa effekten, det vill säga över 90% förbättring i handtremor och handfunktion, erhålls i substrukturerna zona incerta (Zi) och radiatio prelemniscalis (Raprl).

I det tredje delarbetet följs 21 opererade patienter. Man ser en 95% minskning av skakningar i handen, en 87% förbättring i handfunktionen och en 66% förbättring i allmän daglig livsföring (ADL).

Det fjärde delarbetet analyserar möjliga prognostiska faktorer. I studien analyseras samband mellan ålder, kön, grad av tremor ochoperationens utfall. Inget samband mellan operationsresultat och kön kunde fastställas. Den absoluta tremorreduktionen korrelerade med graden av tremor innan operation, det vill säga ju mer skakningar patienten lider av innan operation, desto mer skakningar kommer hon att ha efter operation.

Det femte delarbetet fokuserar på livskvalitet efter cZi DBS hos patienter med ET. Detta är viktigt eftersom DBS aldrig kommer att bli en livräddande
behandling och det är av stor vikt att verifiera att den bidrar till en förbättring av livskvaliteten. Vad gäller tremor uppnåddes mycket goda resultat. Det generella livskvalitetsformuläret påvisade inga statistiskt signifikanta förändringar. Detta är sannolikt pga att denna skala mäter många andra aspekter än bara det relaterat till ett symptom. Denna diskrepans mellan den goda effekten på skakningarna och den modesta förändringen i livskvalitetsskalorna torde tala för att det behövs en mer avancerad utvärdering av livskvalitet än vad dessa relativt enkla instrument kan ge.

Sammanfattningsvis är våra slutsatser att DBS i cZi verkar vara en säker och effektiv behandling för ET.
Introduction

“For all knowledge and wonder (which is the seed of knowledge) is an impression of pleasure itself.”

Francis Bacon, The Advancement of Learning, 1605

Essential Tremor

Descriptions of tremor range as far back as Galen’s definition in the second century and involuntary movement during action and rest were described as two different entities in the 17th and 18th centuries by de la Boë Sylvius and van Sweiten. Tremor as a symptom was described in the 19th century by Charcot in both drawings and writing, although the tremor he refers to seems to be Parkinsonian tremor. He also made distinctions between multiple sclerosis (MS) tremor, Parkinsonian tremor and tremor of other causes such as mercury poisoning.

The term essential tremor (ET) was first used by Italian Buressi (1874) to describe an 18-year-old man with severe, isolated action tremor. A few years later similar cases were described and such nomenclature as tremor essenziale congenito (congenital essential tremor), essentieller tremor (essential tremor) and tremblement essential héréditaire (hereditary essential tremor) were suggested. By the early 20th century the term began to appear in medical literature with greater frequency.

Tremor is defined as an involuntary, rhythmic, oscillatory contraction of agonist and antagonist muscles. ET is the most common movement disorder with prevalence estimates in Europe ranging from 1.2 to 5.6% of the adult population. A recent review by Deuschl et al rates its prevalence to up to 9% in certain populations. The incidence increases with age and the highest frequency of ET is found among patients in their 80’s. The disease is characterized by tremor of action and posture, maintaining a frequency of 4-12 hertz (Hz) and worsening with emotional stress. The tremor frequency decreases with time by 0.06-0.08 Hz per year. The severity of the disease can vary widely and most patients with ET are neither diagnosed nor treated. The tremor may affect voice, head, and legs, but it is most common in the upper extremities. The tremor of the hands can be severely disabling, making such tasks as eating, drinking, and writing more or less impossible to perform. Community-based studies report functional impairment due to tremor in 60-73% of patients.

The view of ET as a monosymptomatic disease appears to be changing toward a view of ET as a polysymptomatic disease with pancebellar deficits. The presenting symptom is always tremor, but lately studies have shown that patients often develop other signs as well. Cerebellar dysfunction such as
impaired tandem walking, upper-extremity intention tremor, target overshoot, oculomotor abnormalities, abnormal motor learning, and abnormal rhythm generation are noted in advanced cases. Other symptoms that have been reported are dementia, olfactory loss, and hearing loss, and the cerebellar dysfunction is further believed to be the cause of differences in personality profile and cognitive function among this group. The relationship between ET and dementia is still a controversial issue.

The condition is to a high degree also socially stigmatizing, leading to avoidance of any motor performance involving the hands in public settings and often leading to isolation of the patient. Advanced forms of ET can therefore negatively affect quality of life (QoL).

The pathophysiology of ET remains unknown. Two pathophysiological hypotheses have been proposed. The first suggests that genetic abnormalities together with non-genetic factors lead to neurodegeneration and tremor. The second suggests that genetic abnormalities cause dynamic oscillatory disturbances in the motor system assuming that ET is not a neurodegenerative disease. A positive family history is found in 20-50% of cases, but a clear Mendelian pattern has not been seen. In young onset cases the positive family history can be up to 80%. A gene variant (HS1-BP3) on chromosome 2 has been linked to familial ET. Recent studies have shown a link between two intronic sequence variants in the LINGO1 (leucine-rich repeat and Ig domain containing 1) gene to be associated with ET. LINGO1 is a protein that is involved in the complex regulation of myelination in the central nervous system.

No clear histopathological abnormalities are linked to ET. However, pathological studies have implied two different pathological patterns that might prevail in ET: one with degenerative changes in the cerebellum leading to a reduced number of Purkinje cells and another with Lewy bodies in the locus coeruleus of the brainstem. One theory has been that tremor is generated in an aberrant central oscillator in the inferior olive. The olivocerebellar oscillations would then be transmitted via the cerebellothalamocortical pathway, traversing structures that all are known to be involved in ET. However, the peripheral tremor oscillations in different limbs are not similar and theories about several different central oscillators contributing to tremor have been presented.

The diagnosis of ET is based on neurologic history and clinical examination. No diagnostic biochemical marker or a specific radiological finding is available to facilitate the diagnosis. There are two different sets of clinical criteria for the diagnosis of ET. The Movement Disorder Society (MDS) considers isolated head tremor in the absence of dystonic posturing to be a variant of ET. The Tremor Investigation Group (TRIG) overlooks head tremor and requires at least a five-year history of hand tremor to ensure that the patient will not develop any symptoms of another disease. Despite the existence of these diagnostic tools,
misdiagnosis is common, since dystonic tremor, PD, and task-specific tremors can be mistaken for ET.\textsuperscript{39,40}

Even though medication might be effective in the mild forms of the disease, approximately 50\% of the patient population proves to be refractory to pharmacological treatment.\textsuperscript{41,42} Drugs known to be efficacious (propranolol and primidone) produce a mean tremor reduction of 50\%.\textsuperscript{11} Although the neurophysiological origin of ET continues to be debated within the scientific community, there remains a sustained need to address the limitations of current pharmacological approaches to the treatment of ET. In severe cases functional stereotactic neurosurgery might be regarded as an alternative to pharmacological treatment.

\textbf{A Brief History of Stereotactic Functional Neurosurgery}

The first attempt at three-dimensional imaging of the human brain was made by Andres Vesalius in 1543 in his “De Humani Corporis Fabrica” as well as by Leonardo da Vinci. The first atlas demonstrating the layered anatomy of the human brain was published in 1583 by George Bartish.\textsuperscript{43} The cerebral topometry was developed by Vicq D’Azyr, who published life-size colored engravings of the brain as well as measurements of individual brain structures. The use of topometry marked the beginning of detailed brain atlases.\textsuperscript{44} In the 19th century the theory of certain brain structures being linked to specific functions prevailed and surgeons started targeting areas of the brain from certain reference structures on the skull.

The cartesian coordinate system, enabling the identification of any given point in space in relation to three intersecting planes, was based on the work of Descartes in the early 17th century.\textsuperscript{45,46} Later Horsley and Clarke constructed brain atlases based on the cartesian coordinate system.\textsuperscript{47} The three cerebral planes, sagittal, horizontal and coronal, were established by Delmas and Pertuiset in their “Cranio-Cephalic Topometry in Man”.\textsuperscript{44} The use of these cerebral planes made it possible to get the cross-sections to match at certain points, making this atlas unique.

Many different atlases have been constructed in order to facilitate targeting. A major challenge throughout the years has been the variability in the human brain. The Spiegel and Wycis atlas was based on a series of 30 sectioned brains. The Talairach atlas focused on the temporal lobe structures basing their atlas on 90 brains.\textsuperscript{48} This atlas came to be extensively used in clinical studies of patients with epilepsy. In 1959 Schaltenbrand published one of the most detailed and most used stereotactic atlases based on 111 brains.\textsuperscript{1} More than 50 years later this atlas is still widely used. An atlas of the thalamic nuclei was published by Van Buren in 1972.\textsuperscript{49} In recent years some other stereotactic atlases have been produced. Stereotactic atlases have also been produced for the cerebellum and spinal cord. Their use for stereotactic operations has been limited.
Even before this, external frames “encephalometers” had been used on humans. The first one seems to be a frame presented by Zernov in 1889. The frame is reported to have been in frequent clinical use and was later succeeded by a “brain topograph” constructed by Rossolimo. Neither of these two frames were based on cartesian coordinates and are therefore not to be considered strictly stereotactic. In late 19th century France a frame was developed in order to localize intracranial projectiles. It has been reported to have been used a few times and seems to have been a true stereotactic construction.

In 1908 Horsley and Clark presented a frame that has been considered to be the first stereotactic frame. It was attached to the head through plugs into the external meatus and bars resting on the nose and lower orbital rim. Based on the three intersecting planes, stereotactic atlases were constructed for the cat and monkey. Several different modifications of this system were constructed over the following years. Clark patented the idea of a stereotactic frame that could be used in humans in order to “by electrical means or by the placement of radium, relieve pain by coagulation of intracerebral tracts and direct application of drugs and pharmaceuticals into the central nervous system”. This led to the design of a human stereotactic frame in 1918. This frame was however never used and did not contribute to any future development.

The first human stereotactic instrument was presented by Spiegel and Wycis in 1947. Spiegel and Wycis' stereotactic frame, together with their brain atlas, marked a new era in which neurosurgeons could navigate three-dimensionally in the brain and soon a number of different frames were constructed. Initially, the cranial reference points used were the outline of the ventricular system and the calcified pineal gland as visualized on a ventriculogram. The Spiegel and Wycis brain atlas was based on internal landmarks that were identified during pneumoencephalography. It was partly a further development of the Horsley and Clark frame. These landmarks were later abandoned for the use of an anterior commissure - posterior commissure (AC-PC) plane suggested by Talairach et al.

Before stereotactic techniques tremor had been treated with open neurosurgery, described by Horsley as early as 1886. Bucy excised cortical areas 4 and 6 and reported tremor relief. Unfortunately, the procedure was linked to a 10% mortality rate. Open surgery with lesioning of the pyramidal tract was also attempted. In 1908 Horsley and Clarke reported on physiologic observations following production of lesions in the dentate nucleus of the monkey. In that paper the authors state “to further progress was to find some method which would satisfy these conditions, viz., a means of producing lesions which should be accurate in position, limited to any desired degree in extent, and involving as little injury as possible to other structures.”
The first stereotactic procedure in a human, a “stereoecephalamtomy”, was reported by Spiegel and Wycis in 1947. They injected alcohol into the pallidum and dorsomedian nucleus in a patient with chorea and noticed a significant clinical benefit. They soon modified their technique to the use of direct current as Horsley and Clarke had described. With the introduction of stereotactic surgery, mortality decreased from 15% in the pre-stereotactic era to 2% within a year and less than 1% by the second year.

Initially, lesions were produced in the pallidum (pallidotomy). The effect on tremor was not optimal and lesional procedures in the thalamus (thalamotomy) were introduced in 1954 by Hassler. At first they were used in the treatment of Parkinsonian tremor, but they were also applied later on to ET. Different targets came to be explored during the following years and it seems that the intended targets often varied substantially between different surgeons. The subthalamic region was a lesional target for ET and Parkinson’s disease (PD) and other movement disorders in many clinical centers. Even though the ventrolateral thalamus was the target of choice in ET, the subthalamic area was targeted increasingly from the 1960s and onward. The subthalamic region was defined to consist of the zona incerta (Zi), the prelemniscal radiation (Raprl), the prerubral area and the field of Forel. Often the lesions in the field of Forel were described as campotomies.

Other targets in proximity to the subthalamic area have been used. Meyers performed substantia nigrotomies but later on moved his target to Forel field H. The same area was later targeted by Spiegel and Wycis who described that the best effect was achieved at the deepest level of the target, an area which would probably affect field of Forel H1 (H1), field of Forel H2 (H2), and Zi. Bertrand, Wertheimer and Andy also had targets in this area. During the 1960s the posterior subthalamic area (PSA) was frequently explored and over the years, many publications have described and evaluated the effect of lesions in the PSA in patients with ET.

When L-dopa became available in 1968 it was thought that movement disorders could be managed medically and in many places stereotactic surgery was abandoned. The field of stereotactic surgery was reawakened by Laitinen et al. in the early 1990s. The resurgence in stereotactic activity was also facilitated by computed tomography (CT), which was introduced in 1973. The irreversibility of lesional procedures led Benabid to introduce in 1987 deep brain stimulation (DBS) as a new reversible concept for treating movement disorders. However, attempts to treat movement disorder with pacemakers had been made before. Following the example of Benabid, the ventrolateral thalamus (Vim) quickly became the target of preference in the treatment of ET.

Many studies showed Vim DBS to be linked to fewer complications than thalamotomies. Since the late 1990s Vim DBS has been considered to be the golden standard and it has virtually replaced thalamotomies.
The Motor System

“... to move things is all that mankind can do ... for such the sole executant is muscle, whether in whispering a syllable or in felling a forest.”

Charles Sherrington, Linacre Lecture, 1924

The motor system keeps on developing for the first 15 years through maturation of neuronal circuitry and by learning through different activities. The coordination of different movements and postures is a difficult task to master, with hundreds of different muscles taking part in a coordinated fashion. The motor neurons and motor units are the basic components of the motor system. The motor neurons control different muscles and are located in different motor nuclei in the brain stem and along the spinal cord. Motor neurons are activated by descending tracts from the forebrain and brainstem and by interneurons. Sensory receptors are important in movement control. Sensory signals from a number of different receptor systems help detect and counteract any disturbance in body position during standing or physical activity.

The hierarchically uppermost center for movement control is the cerebral cortex. The motor impulses for voluntary movement are mainly generated in the primary motor cortex (precentral gyrus, Broadman area 4) and in the first motor neuron in the adjacent cortical area. The impulses descend in the long fiber pathways, mainly corticonuclear and corticospinal tracts (also known as pyramidal pathway), via the brainstem down to the anterior horn of the spinal cord where synaptic contact with the second motor neuron is established. In addition to the pyramidal tract, the premotor area (Broadman area 6) and basal ganglia also participate in neural movement control. The basal ganglia are subcortical interconnected nuclei, consisting of the striatum, the subthalamic nucleus (STN), globus pallidus (Gp, consisting of internal and external segments), and substantia nigra (SN, consisting of pars compacta, SNc and pars reticularis, SNr) in the forebrain, midbrain and diencephalon.

The neural connections between the basal ganglia and other regions are not yet completely understood. It seems that the striatum and the STN are the main input structures and the internal globus pallidus (Gpi) and SNr are the output nuclei. The basal ganglia function as an accessory movement center for initiation and modulation of movement, in the expression of emotion and in the integration of motor and sensory impulses and in cognitive processes. Their main role appears to be initiation and facilitation of voluntary movement. Moreover, they use proprioceptive feedback for the periphery so that the movement is subject to ongoing refinement.
The basal ganglia receive a broad spectrum of cortical inputs, which are processed in the basal ganglia circuitry to produce inhibitory output to the frontal lobes, thalamus and brain stem, thus completing a feedback loop. Most of the input comes from the cortex, but thalamic nuclei (centromedian) also provide strong input to basal ganglia, mostly striatum. STN receives input from the motor, premotor, and supplementary motor cortex and from the frontal eye fields. The feedback interaction between STN and the external Globus pallidus (Gpe), direct cortical inputs to STN and the interaction of additional nuclei such as the pedunculopontine nucleus (Ppd) and reticular thalamus complicate our understanding of these networks. In addition, the presented models do not take into account the pattern and synchrony of neural activity in each of the interacting nuclei.

The cortico-striato-pallido-thalamo-cortical pathway leads topographically organized information from the motor and sensory cortex to the striatum. From here the basal ganglionic circuit divides into two monosynaptic parts: the direct and the indirect pathway. The direct pathway, using gamma-aminobutyric acid (GABA) as transmitter and substance P as co-transmitter, runs to the Gpi and further to the thalamus, which completes the loop to the cortex. The indirect pathway, using GABA and encephalin, runs to the Gpe from where the projections go further to the STN, which sends a glutamatergic projection to the Gpi which conveys the projection to the cortex. The overall effect on the cortex of the direct pathway is considered to be excitatory and of the indirect pathway inhibitory. The antagonistic functions of the direct and indirect pathways are modulated by the dopamine producing SNc.

Anatomical studies have implied, however, that the separation of direct and indirect pathways might be less than initially reported due to extensive collaterals. Through neurotransmitters and baseline activity of neurons in the basal ganglia network, activation of the direct or indirect pathways can produce functionally opposite effects on thalamic output. The SNc is thought to modulate these pathways through dopaminergic projections via the ventral anterior and ventrolateral thalamus, all the time maintaining the neuronal specificity and somatotopy. The pallidothalamic tract originates in the Gpi and consists of the ansa lenticularis and fasciculus lenticularis (coursing through H2). These merge into the fasciculus thalamicus or H1, before entering the thalamus.

The cerebellothalamic/dentatorubrothalamic tract connects deep cerebellar nuclei (dentate, emboliform and globose) with the thalamus and traverses the superior cerebellar peduncle to decussate at the level of the upper pons or inferior colliculus and pass right anterior to the contralateral nucleus ruber before reaching the thalamus. These two tracts do not converge in the subthalamic region. The cerebellothalamic tract in itself forms the superior cerebellar peduncle and is the largest efferent connection from the cerebellum. A recent case report linking diffusion tension imaging fiber tracking with postoperative CT has shown involvement of the cerebellothalamic tract in tremor reduction after DBS. This theory is supported by extensive research by Plaha et al., who have suggested that tremor control might be more
efficient in the caudal Zona incerta (cZi) where the cerebellothalamic fibers are more densely packed.\textsuperscript{151-153} The cerebellothalamic tract corresponds in large part to Hassler’s prelemniscal radiation (Raprl) and to ther prerubral field or the field H of Forel.\textsuperscript{154} This could be an explanation to why stimulation in these areas give tremor reduction.

The idea of cerebellar and basal ganglia output converging at the thalamic level has recently been challenged by views describing basal ganglia as components in parallel re-entrant loops where information is returned to the cortex via the thalamus.\textsuperscript{148} Currently, there are several models regarding the motor system, the pathophysiology behind different movement disorders, and the mechanism of action of DBS. Presently, there are four hypotheses that attempt to explain the therapeutic effect of DBS.

1. \textit{Depolarization blockade}, stimulation-induced alterations in the activation of voltage-gated currents that block neural output near the stimulating electrode.\textsuperscript{155}
2. \textit{Synaptic inhibition}, indirect inhibition of neuronal output via activation of axon terminals that make synaptic connections with neurons near the stimulating electrode.\textsuperscript{156}
3. \textit{Synaptic depression}, synaptic transmission failure of the efferent output of the stimulated neuron. This is a result of transmitter depletion.\textsuperscript{157}
4. \textit{Simulation-induced disruption} of pathological network activity.\textsuperscript{158}

Depolarization blockade and synaptic inhibition are supported by single-unit recordings, although the functional effect of this might have limited significance in the therapeutic effect of DBS.
Structures and Targets

“'Contrariwise,” continued Tweedleddee, “if it was so, it might be; and if it were so, it would be; but as it isn’t, it ain’t. That’s all logic.”

Lewis Carroll, Through the Looking-Glass, 1871

Nomenclature

The literature about thalamic surgery can be quite confusing. Neurosurgeons tend to use the Schaltenbrand atlas with Hassler nomenclature of the thalamus. Neuroanatomists use different nomenclatures based entirely on cytoarchitectonic subdivisions and transfer of knowledge by analogy from the monkey to man. In this thesis I have tried to consistently use the Hassler terminology or the nomenclature that has been most widely used in scientific publications. In the cases where an alternative nomenclature is more common than the Hassler terminology in Schaltenbrand, the Hassler term has been written in cursive, and an explanation has been given.

Thalamus

The thalamus is an 3 x 1.5cm ovoid paired structure flanking the third ventricle. It is a conglomerate of numerous distinct nuclei, each with its own function and connections. Each thalamus is often divided into three regions (anterior, ventrolateral, and medial) or four regions (anterior, medial, ventrolateral, and posterior) based on the anatomical divisions created by the internal medullary lamina. These can be further subdivided into 120 functional and cytological groups. The ventrolateral thalamus contains nearly all the nuclei intimately involved in sensorimotor function. Furthermore, it is the largest subcortical collecting point for exteroceptive and proprioceptive sensory impulses and serves as a center for integration and coordination. The motor thalamus can be further subdivided into distinct relays and through the thalamic reciprocal feedback loops it modulates motor function. Gpi projects to the anterior part of the ventrolateral thalamus, the anterior ventrooral nucleus (Voa), and the posterior ventrooral nucleus (Vop), which in their turn project toward the supplementary motor cortex. The cerebellum projects to the posterior part of the ventrolateral thalamus, which projects to the motor cortex and arcuate premotor area.

Reciprocal corticothalamic projections occur between the nucleus ventralis intermedius (Vim) and the motor cortex, as well as the ventrolateral/ventral anterior thalamus to the secondary motor cortex (premotor cortex, posterior
parietal cortex, and supplementary motor area.) The majority of thalamic nuclei projecting to the cortex use glutamate as their neurotransmitter. Another important part of this structure is the reticular nucleus of the thalamus (RT), which contains reticular neurons which give a widespread inhibitory input to cells in the entire thalamus. Thalamocortical projection neurons provide direct input to reticular neurons, thus generating tight feedback loops and information processing. One of the theories behind targeting the thalamus has been based on the assumption of a dysfunctional thalamocortical system, with thalamocortical dysrhythmia following thalamic cell deactivation. In some clinical studies the highest proportion of cells exhibiting tremor-frequency activity was found to be in the Vim and in the Vop and VoA. This has been one argument for using Vim DBS for ET.

**Posterior Subthalamic Area**

Many different terms have come to be used in the literature on PSA. These terms are, with some variants: the subthalamic area, the PSA, the posterior subthalamic white matter, the Zi and the Raprl. Zi and Raprl are specific structures within the PSA which have been specifically targeted by some groups. Neither of these two structures is distinguishable on MRI, and since it is not clear which structures in the area might contribute to the beneficial effect, we have chosen to call the area PSA. Recently, we have changed the name of our target to a specific substructure in PSA, the lower posterior part of Zi, which is denoted as cZi. In order to avoid confusing the reader, in this thesis our target will be referred to as cZi and the term PSA will encompass both Zi and Raprl.

The PSA is bounded anteriorly by the posterior border of the subthalamic nucleus, inferiorly by the dorsal border of the SN, superiorly by the ventral thalamic nuclei, posteromedially by the anterolateral border of the nucleus ruber, posteriorly by the medial lemniscus (Lm), posterolaterally by the ventrocaudal nucleus, and laterally by the posterior limb of the internal capsule (IC). The PSA is considered to include the Zona incerta (Zi), Raprl, H1 and H2. The H1 and H2 lie in close proximity to the STN. The H2 rides over the dorsal part of STN, Zi separating H2 from the more dorsal H1. Anterior to the nucleus ruber, the posteromedial portion of the H1 and H2 fields are in continuity with the field H, which is considered to be located outside the PSA.

In the older literature a somatotopic organization within the PSA has been suggested, with the leg in the lateral part, the head being represented in the medial part and the hand in the middle. This has not been confirmed in more modern studies. Even though the pathophysiology of tremor generation is not clear, it has been suggested that the cerebello-thalamic connections in the PSA play an important role. It has also been stated that fibers and neurons, especially those related to proximal muscles, are more concentrated in the PSA than in the Vim. This would imply that it might be easier to achieve an effect on tremor with an intervention in the PSA than in the Vim.
**Zona Incerta**

Zi is an embryological derivative of the ventral thalamus. Areas within Zi with specific morphological and functional characteristics have been found. The small cellular nucleus of Zi is located on the dorsal and posterior aspect of the STN, between H1 (dorsally), H2 (ventrally), and H (medially). It is connected to the cerebellum, brainstem, reticular formation, Ppd, SNr, Gpi, superior colliculum, thalamus, cerebral cortex, and the spinal cord through reciprocal communication. It can be divided into areas (rostral, caudal, ventral, dorsal). The caudal component is thought to be the motor sector. The rostral part is thought to have a visceral control function, the dorsal an arousal function, and the ventral a function in orientating eye/head movements.

**Fig 1.** Schematic drawing based on the Schaltenbrand and Wahren atlas, demonstrating selected structures in the PSA and its surroundings. A and B correspond to horizontal slices H.v -1.5 and -3.5, respectively; C and D correspond to coronal slices F.p 5.0 and 7.0; E and F correspond to sagittal slices S.I 10.5 and 13.0. Cpip, internal capsule, posterior limb; Hs, field Hs of Forel; Sth, subthalamic nucleus; Ll, lateral lemniscus; Lm, medial lemniscus; Ni, substantia nigra; Ppd, peripeduncular nucleus; Q, fasciculus Q; Raprl, prelemniscal radiation; Ru, nucleus ruber; Vim.e, external Vim; Vim.i, internal Vim; Voa, nucleus ventro-oralis anterior of the thalamus; Vop, nucleus ventro-oralis posterior of the thalamus; Zi, Zona incerta (modified from, Schaltenbrand G, Wahren W: Atlas for Stereotaxy of the Human Brain. Stuttgart, Thieme, 1977 Reprinted from Blomstedt et al, Neurosurgery with the kind permission of the publisher.)

Despite the anatomical proximity, there is little or no reciprocal connection between Zi and STN. Zi is an important hub within both thalamocortico-basal
ganglia and cerebello-thalamocortical ones and connects motor behavior with environmental sensory input.\textsuperscript{180} The neurons are mainly GABAergic and hence inhibitory, while some projections are glutamatergic and excitatory or dopaminergic.\textsuperscript{181,182} In animals lesions in the Zi produced effects on vegetative function, attention, arousal and motor behavior.\textsuperscript{180}

Zi plays a role in gating unwanted sensory input by inhibition of thalamic neurons; similar mechanisms are thought to mediate its other sensorimotor functions.\textsuperscript{179,183} Zi has been considered to have a role in oscillatory networks (among them, the cerebellothalamic tract) including, the thalamus, cerebellum and basal ganglia and hence being a part of generation of tremor in Parkinson’s disease and ET.\textsuperscript{184}

\textbf{Prelemniscal Radiation}

The Raprl is a fiber bundle located posteriorly to the STN, separated from it by the intervening Zi. It consists of ascending cerebello-thalamic fibers as well as of fibers from the mesencephalic reticular formation, which projects to the thalamus.\textsuperscript{154} Continuous stimulation of the Raprl is believed to result in increased inhibition within local circuits and improves contralateral tremor.\textsuperscript{185} These observations suggest that the Raprl is functionally related to the mesencephalic reticular formation and plays a role in tremor and muscle tone within the prevailing attentional context.\textsuperscript{185,186}
Background of the Present Study

“Remember what Bilbo used to say: It’s a dangerous business, Frodo, going out your door. You step onto the road, and if you don’t keep your feet, there’s no knowing where you might be swept off to.”

J.R.R. Tolkien, Lord of the Rings, 1952

ET is a common condition, often leading to a significant handicap and reduction in the quality of life (QoL). There are several challenges in the clinical treatment of ET. The effect of pharmacotherapy is generally poor, only approximately 50% of the patients respond to medical therapy. The current surgical treatment of choice is Vim DBS. With Vim DBS the results are poor in about 20% of the cases, and even in the successful cases there is often a decrease in effect over time. There are also studies stating that proximal tremor and the action component of distal tremor respond poorly to Vim DBS. Data from the lesional era have suggested the PSA to be a good target for the treatment of tremor. Lately several studies have demonstrated excellent results of DBS in the PSA. These findings have encouraged us to assess the efficacy in a one year follow-up.

PSA consists of several substructures; many of them have been targeted in previous studies. If stimulation in the PSA is favourable compared to the Vim, studies determining the optimal localization for DBS in the PSA and providing a map for the peroperative evaluation of the electrode position are needed.

In DBS for ET our clinical impression has often been that younger patients as well as patients with more severe tremor get better results from surgery. We have also noted that women have been less frequently operated upon, even though ET is equally distributed between males and females. Since there is a lack of studies regarding prognostic factors for DBS, we have decided to evaluate this aspect.

Compared to an age-matched healthy population, the ET population is known to experience a poorer QoL, especially in aspects related to psychosocial functioning. Although there are some studies evaluating tremor after PSA DBS in ET, there is, to our knowledge only one study evaluating the QoL after surgery. Since DBS cannot be seen as a curative treatment it seems essential that its role in improving QoL should be established.

DBS has many advantages and is often considered to be a safer technique with regards to reversibility and fewer risks, especially in bilateral procedures. The implanted hardware is linked to problems such as high cost, risk of infection and malfunction. With the implantation of hardware the patient also commits to lifelong follow-ups including changing of the implantable pulse generator (IPG) and outpatient clinic attendance to modulate the stimulation. The use of lesional
surgery has been discussed as an alternative in certain well-selected cases.\textsuperscript{195} Although there are some modern studies concerning the long-term effect of lesional surgery in ET, there is a need for further evaluation of the lesional technique.\textsuperscript{99,137,138,196-201} For that reason, a retrospective follow-up of thalamotomies, especially regarding the long term effects, has been performed.
Aims

The specific aims of this thesis are:

To evaluate the effect of DBS in the PSA.

To attempt to compare the efficacy of the different targets for DBS in ET.

To investigate whether patients operated on a priori in the Vim are in reality sometimes stimulated in the PSA.

To evaluate the effect of thalamic/subthalamic DBS in relation to the position of the electrode, and to identify the structures affected by the stimulation.

To assess the quality of life in patients treated with PSA DBS for ET.

To evaluate the possible influence of gender, age and severity of disease on the outcome in DBS for ET.

To retrospectively analyze the outcome of thalamotomy in the treatment of ET, with special consideration to the size and localization of the lesion.
Material and Methods

“Brain, n. An apparatus with which we think we think.”

Ambrose Bierce, The Devils’ Dictionary

Study I

Patients operated with lesions in the ventrolateral thalamus for ET at our department during the period 1972-1999 were followed up in a long-term retrospective study. The patients were identified from operation records. Patients under the age of 80, without any other neurological disorders were offered participation. In total, 107 operations were identified; on excluding reoperations, 93 patients were identified. Of this group 39 patients were deceased, four patients had moved to different administrative regions and 39 were over 80 years old. Nine suitable patients (five females, four males) were identified; all of these had been operated on during the years 1981-1996. None of them were recorded in the charts as having voice tremor. One of the patients had bilateral lesions performed in a staged procedure. In one case an ipsilateral re-thalamotomy was performed. The mean age at follow-up was 69.3 ± 10.7 years and the mean follow-up time was 20.8 ± 5.2 years. The surgical data were extracted from operation reports.

The patients were evaluated at the outpatient clinic of our department. They were examined with a full neurological assessment as well as tremor assessment using the ETRS. The neurological assessment was performed according to the written standard procedure at our department. After taking the history, the patients were also actively interrogated about the experience of side effects that are known to be related to lesional surgery. These side effects were: cerebellar symptoms (dysarthria, disequilibrium, apraxia, ataxia, gait disturbance)99,136,138,198-203, motor weakness contralateral to the lesion99,197, general speech difficulties35,99,196,204,205, facial numbness or weakness99,137,198,206, and cognitive impairment.137,198 Cognition was tested using a verbal fluency test that assesses the speed and flexibility of verbal thought processes.207,208 Balance was assessed by the Berg’s Balance Score (BBS).209-211 Tandem movement was tested by assessing tandem gait. Abnormal tandem walking was defined as more than three missteps per minute.212 The QoL was investigated using the Quality of Life in Essential Tremor (QUEST) and the generic Short Form (SF-36) forms.213,214 Speech was recorded and evaluated by five speech pathologists. The frequency of different speech pathologies such as dysarthria, dysphasia, dysphonia, and voice tremor, was to be recorded. The voice samples consisted of a sustained phonation task, self-assessment, and the reading of a standard text. The recordings were made on a Marantz PMD660 media player with microphone AKG C420 with a sampling rate of 44 100 - 48 000Hz. The microphone was located in a headset
and placed 10 cm from the patient's mouth. One patient was excluded from the evaluation because of poor quality of the recording.

The radiological evaluation of the lesion size and the proximity to neuroanatomical structures was done using magnet resonance images (MRI). In one case the MRI was not possible to perform due to claustrophobia, instead a CT scan was performed. The volume was approximated by assuming the shape of the lesion to be spherical and using the geometric formula \( \frac{4}{3}\pi r^3 \). The coordinates of the lesion were calculated using the FrameLink® planning station (Medtronic®).

**Study II**

The electrode contact location was analyzed in 36 patients (19 PSA /17Vim, 44 electrodes) in this retrospective non-randomized study. Four patients (two Vim and two PSA) had bilateral electrodes. The patients were evaluated with regard to ETRS (Item 5/6, hand tremor, and Items 11-14, hand function) one year after surgery in the PSA group and after a mean period of 66 ± 36 months in the Vim group. The tremor score on-stimulation was compared to the score off-stimulation at the same evaluation. The evaluation was conducted under standardized settings with increasing voltage until the best effect was achieved. The contacts yielding more than 90% tremor reduction were arbitrarily defined as an optimal location.

The areas yielding the best tremor alleviation are presented as topographical charts plotted onto neuroanatomical structures. The stereotactic coordinates of all contacts were ascertained by software calculations (FrameLink®, Medtronic) using the postoperative computed tomography (CT). These were plotted onto the Schaltenbrand stereotactic atlas.\(^1\) The optimal contacts were plotted onto a contour plot using Matlab® software. These contours then serve to define areas that are considered to be optimal stimulation targets.

**Study III**

Twenty-one patients operated on with PSA DBS for ET at our department were followed up in a prospective one-year follow-up. The group consisted of seven women and 14 men. Two of the procedures were bilateral. Four of the early patients had an additional ipsilateral electrode in the PSA due to suspected suboptimal positioning of the first electrode. Two patients had bilateral electrodes and four had an extra ipsilateral electrode implanted (one Vim, three STN) due to participation in another study. No patient had simultaneous stimulation of two ipsilateral electrodes.

After surgery all contacts were evaluated and the contact achieving the best tremor alleviation was chosen for chronic stimulation. The extent of tremor was
evaluated on the ETRS before surgery, after surgery without the stimulation on (off-stimulation) and after surgery with stimulation on (on-stimulation).

**Study IV**

Correlational data were collected from 68 patients (34 Vim DBS/34 PSA DBS) in this nonrandomized longitudinal sequential study. Six of the patients had bilateral DBS. The tremor was analyzed using Item 5/6 (hand tremor) and Items 11-14 (hand function) for the treated side. These were extracted from the ETRS score before and after surgery. The PSA group was evaluated one year after surgery and the Vim group was evaluated 28 ± 24 months after surgery.

**Study V**

QoL was followed up in this prospective study of 16 consecutive patients. Two procedures were bilateral. All but one patient had the surgery performed on their dominant side.

The evaluation was performed at baseline as well as one year after surgery. Tremor was evaluated using ETRS (both on- and off-stimulation) and QoL was assessed using QUEST and SF-36 forms.

**Description of the Surgical Procedure**

Study I is the only study in which lesional surgery was performed. In all patients a preoperative stereotactic CT-scan was performed. The Laitinen stereoadapter was used and the surgery was performed with the Laitinen stereotactic frame. A peroperative ventriculography was performed in three of the operations. Lesioning was performed using 65-75°C, stimulation time being 10-70 seconds using, on average, 2.1 ± 1.1 lesions. Using two different level lesions was the usual approach at our department. The lesion was performed with close monitoring of the patients' response.

In Studies II, III, IV, and V implantation of DBS was the surgical method. Before surgery the patients underwent stereotactic CT and/or MRI scans wearing the Leksell or Laitinen stereotactic frame. Laitinen frame was used for most of the patients with Vim DBS, since 2004 the Leksell frame has been used. All PSA DBS were performed with the Leksell frame. FrameLink® software was used in calculations of the coordinates for target and trajectory when Leksell frame was used. The target in the PSA was identified on transaxial T2-weighted MRI images at the maximal diameter of the nucleus ruber, slightly
posterior-medial to the tail of the STN. The target in the Vim was placed at the level of the intercommissural line (ICL), 13-15mm lateral to the midline of the third ventricle, 6-7 mm anterior to the PC. 

During the surgery the patient was awake and the implantation of the electrode was performed under local anesthesia. The whole head was shaved and prophylactic antibiotic, usually a second generation cephalosporin, was administered prior to and during three days after surgery. Most of the burrholes were made with a hand drill, placed 2.5-4cm from the midline at the level of the coronal suture. The burr-hole measured 14mm in diameter. The durotomy and corticotomy were performed using monopolar cauterization. A radiofrequency electrode was used for track making and, in some cases, impedance measuring. The permanent electrode (Medtronic DBS electrode 3387® or 3389®) was employed for macrostimulation. No microelectrode recording was made. All four contacts (contacts 0-3, contact 0 being the most distal) of the electrode were evaluated and contact 1 was aimed at being placed at the level achieving the best response. This meant that, in general, an area 7 mm above and 2-4 mm below the target was explored.

A stereotactic CT for image fusion (in cases where FrameLink® was used) and identification of electrode position was performed before removing the stereotactic frame. In cases where the Laitinen frame was used the CT was performed after the removal of the frame. Implantation of the implantable pulse generator (IPG) (Itrel II®, Kinetra®, Soletra® or Activa PC®, Medtronic Minneapolis, MN USA) in a subcutaneous pocket under the clavicle was performed under general anesthesia.

**Statistics**

The statistics in all the studies are reported as mean values and standard deviations. P values equal to or less than 0.05 are considered to be statistically significant. All statistical calculations are performed using SPSS®, StatView® or JMP® software.

In Study I correlation was assessed by regression analysis. The lesion volume is reported as mm³ and the standard deviation as well as the range. The location of the lesion is reported as mean X (laterality), Y (anterio-posterior) and Z (superior-inferior) locations, standard deviation and range.

In Study III statistically significant differences are determined using the non-parametric Friedman’s test and the Wilcoxon signed rank test as a post-hoc test.

In Study IV regression analysis was used in determining predicting factors including age, gender and severity of disease. Correlations were analyzed using Pearson test for continuous variables and the Spearman’s rho test was
employed for discrete variables. Logistic regression analysis was used for assessment of predicting Wilcoxon’s signed rank was employed in paired non-parametric results and Wilcoxon’s rank sum test was used in unpaired results. A paired or unpaired two-tailed t-test was performed when appropriate.

The statistical test used in Study V was Wilcoxon signed-rank and the Bonferroni correction is used as a post hoc test.

**Scales**

**Tremor Scales**

Until 1993 there was no validated tremor scale, and most studies employed ad-hoc scales, thus making comparisons between different trials difficult. The Fahn Tolosa Marine (FTM) rating scale, also called the Essential Tremor Rating Scale (ETRS) was published in 1993 and validated in 2007. ETRS is currently the most frequently used method to quantify tremor in ET.

The ETRS is used in all studies in this thesis. The scale measures and quantifies rest, postural and action tremor in ET. It is divided into three parts (A, B and C), each measuring different aspects of functioning. Part A measures tremor in rest, postural and action settings for nine different parts of the body. Part B measures action tremor in the upper extremities. Part C evaluates impact of tremor on ADL functions and is rated by the patient him/herself. The maximum score of ETRS is 144, Part A being maximally 80 points, B 36 points and part C 28 points. Each subscore is rated from 0 to 4 with 4 being the most severe impact on function and 0 no impact on function.

**Quality of Life Scales**

The SF-36 consists of 36 questions divided into eight subscores: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH). The SF-36 subscores can be collected into two summary subscores, a mental component summary (MCS) calculated from the VT, SF, RE, and MH and a physical component summary (PCS), which is derived from PF, RP, BP, and GH. In this thesis the SF-36 scores were transformed and calculated according to pre-existing standardized algorithms.

The QUEST is an ET-specific questionnaire consisting of 30 items subdivided into five scales: Physical/ADL, Psychosocial, Communication, Hobbies/Leisure and Work/Finances. Each subscore is expressed as a percentage of the total score possible. The summary index of the QUEST scale (QUEST-SI) was calculated according to the developers’ instructions.
Cognitive Assessment

The verbal fluency test used in this thesis has been performed as described by Bäckman et al., and the age-adjusted normal values have been extracted from the same publication. The fluency test consists of four parts, and the patient is given one minute to finish each part. The first part consists of a task where the patient has to name as many words as possible starting with the letter A (Task A). In the second part the patient is instructed to generate as many five-letter words starting with the letter M as possible (Task M). The third part consists of naming as many occupations as possible starting with the letter B (Task B). The fourth and last part consists in naming five lettered animals starting with the letter S (Task S). The examiner added up all the answers. Before commencing the test the patients were instructed about common names or grammatical variations were not accepted as answers.

Measuring Balance

The BBS was developed as a clinical measure of functional balance specifically in older people. The BBS consists of 14 tasks that are each evaluated on a scale of 0 to 4, for a total possible score of 56, indicating no identified balance difficulties. It comprises 14 observable tasks common to everyday life measured in tasks such as sitting, standing, transfer and turning. The scoring is graded such that a score of 0 is assigned if a person is unable to perform a task and a score of 4 is assigned when the task is performed independently.
Results

“Knowledge is power.”

Francis Bacon, Meditationes Sacrae 1597

Study I

Seven out of the nine patients reported some extent of tremor reduction after the surgery. The tremor-free period of time lasted, according to the patients, up to 20 years, all patients with symptom reduction experienced recurrence of tremor after some time. No permanent tremor abolition was seen in this limited material.

<table>
<thead>
<tr>
<th>Table 1. Clinical characteristics of Study I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females/Males</td>
</tr>
<tr>
<td>Age at follow-up</td>
</tr>
<tr>
<td>Follow-up period (years)</td>
</tr>
<tr>
<td>ETRS at follow-up</td>
</tr>
<tr>
<td>Total (max 144)</td>
</tr>
<tr>
<td>Hand tremor and hand function treated side (Items 5/6+ 11 - 14)(max 28)</td>
</tr>
<tr>
<td>Hand tremor and hand function non-treated side (Items 5/6 + 11 - 14)(max 28)</td>
</tr>
<tr>
<td>Bilateral staged procedure</td>
</tr>
<tr>
<td>Reoperation on the same side</td>
</tr>
<tr>
<td>Lesion size (mm³)</td>
</tr>
</tbody>
</table>

Mean coordinates (in relation to mid-commissural point)

<table>
<thead>
<tr>
<th>Center of lesion</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>14.3 ± 2.6</td>
</tr>
<tr>
<td>Y</td>
<td>-4.1 ± 1.6</td>
</tr>
<tr>
<td>Z</td>
<td>1.6 ± 3.0</td>
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<tr>
<td>Superior border</td>
<td></td>
</tr>
<tr>
<td>X</td>
<td>15.9 ± 3.3</td>
</tr>
<tr>
<td>Y</td>
<td>-1.7 ± 3.8</td>
</tr>
<tr>
<td>Z</td>
<td>4.9 ± 2.9</td>
</tr>
<tr>
<td>Inferior border</td>
<td></td>
</tr>
<tr>
<td>X</td>
<td>13.4 ± 2.8</td>
</tr>
<tr>
<td>Y</td>
<td>-4.6 ± 3.2</td>
</tr>
<tr>
<td>Z</td>
<td>-1.1 ± 3.4</td>
</tr>
</tbody>
</table>

When the radiological images were analyzed the mean lesion size was determined to be 39.0 ± 17.3 mm³ (range 12-68). The center of the lesions had the mean coordinates \( X = 14.3 ± 2.6 \) (range 9.9–17.7), \( Y = -4.1 ± 1.6 \) (range -7.4–-2.3), and \( Z = 1.6 ± 3.0 \) (range -1.3–6.4.) These lesions were located in various parts of the thalamus, IC, STN, and the PSA.

Three of the patients reported a balance impairment occurring immediately after the surgery. An age-adjusted objectively measured low-borderline balance affection could be verified in one of these patients. On the BBS the Item “Tandem Standing” generally produced the lowest scores.
Tandem walking was tested during the neurological examination produced abnormal results in eight patients. In this test abnormal results are considered to be more than three missteps in less than one minute.

Cognition, tested by a verbal fluency test, showed a large variation in the age-adjusted results. The difficult task, part S, showed a poor performance, only 27.8% of that expected. On the Tasks M and B, which are considered to be simpler, the group in generally performed better than the reference population. Task A also showed a poor performance.

The speech analysis indicated dysarthria in one patient, abnormal voice quality in five, voice perturbations in four, elevated tone of voice in three, abnormal articulation in three, abnormal speech rate in two, and voice tremor in three. Two of the patients were considered to be free of any perceptually or acoustically identifiable speech or voice impairment.

Both SF-36 and QUEST scores for the group indicate impairment in both the physical and mental QoL. The average scores for the subscales of PF, RP, BP, GH, VT, SF, RE, and MH in SF-36 were lower compared to a healthy Swedish population. According to the QUEST evaluation, the aspects of life exhibiting the most extensive disability were the ADL and psychosocial subscales.

The interrogation concerning the patients’ symptoms revealed that three had endured side effects severe enough to make them regret undergoing the procedure. Nearly all patients experienced side effects. The most troublesome symptoms were reported to be impaired balance, speech difficulties, cognitive impairment, other movement disorders, facial paralysis, ataxia and dysmetria. The subjective symptoms perceived by the patients are listed in Table 2.
<table>
<thead>
<tr>
<th>No.</th>
<th>Patient/sex/age/follow-up years</th>
<th>Side/location/volume/coordinates</th>
<th>Subjective symptoms/ETRS total/ETRS treated hand*/ETRS nontreated hand*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M/61/20</td>
<td>Ds/sup post STN/ PSA/</td>
<td>Tremor recurrence after 10 years/41/20/21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>X3.8,Y=-2.6,Z=5</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>M/55/24</td>
<td>Sin/ant thalamus, Ic/</td>
<td>Transient tremor reduction. Permanent contralateral irregular</td>
</tr>
<tr>
<td></td>
<td></td>
<td>43mm/</td>
<td>jumping movement in arm and leg. Impaired balance, dysarthria,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>X6.7,Y=-5.2,Z=1</td>
<td>hypophonia, ataxia, apraxia, burning sensation in right forearm,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>cognitive impairment (memory, concentration), reduced stress</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>tolerance. Reoperation one year later. 35/6/9</td>
</tr>
<tr>
<td>3</td>
<td>M/76/16</td>
<td>Sin/lat thalamus,STN/</td>
<td>Transient tremor reduction, slight recurrence after 4 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>28mm/</td>
<td>39/10/7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>X7.2,Y=-7.4,Z=0</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>M/75/15</td>
<td>Sin/post thalamus,STN/</td>
<td>No tremor relief. Permanent balance impairment, weakness in</td>
</tr>
<tr>
<td></td>
<td></td>
<td>26mm/</td>
<td>contralateral leg, contralateral ataxia, gait disturbances,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>X3.1,Y=-3.4,Z=9</td>
<td>dysphagia, speech difficulties (dysarthria, hypophonia, dystonic speech).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dysphagia. 54/14/16</td>
</tr>
<tr>
<td>5</td>
<td>F/78/14</td>
<td>Dx/Vim/</td>
<td>Tremor recurrence to a certain degree. 50/18/13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>52mm/</td>
<td>X12.6,Y=-5.2,Z=4.2</td>
</tr>
<tr>
<td>6</td>
<td>F/80/20</td>
<td>Dx/Ic/</td>
<td>Transient tremor reduction. Permanent numbness in contralateral</td>
</tr>
<tr>
<td></td>
<td></td>
<td>28mm/</td>
<td>arm, leg contralateral leg. 60/13/14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>X17.7,Y=-5.5,Z=0.5</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>F/78/23</td>
<td>Sin/Lat post STN,Ic/</td>
<td>No tremor relief. Permanent contralateral facial paralysis,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>28mm/</td>
<td>ataxia, apraxia, dysmetria, reduced fine motor function.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>X3.5,Y=-2.6,Z=1.3</td>
<td>65/21/23</td>
</tr>
<tr>
<td>8</td>
<td>F/69/26</td>
<td>Sin/thalamus,Ic/</td>
<td>Tremor recurrence 20 years after surgery. Permanent balance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>48mm/</td>
<td>impairment, ataxia. 55/18/20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>X16.8,Y=-2.3,Z=6.4</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>F/52/29</td>
<td>Dx/Lat dors thalamus/</td>
<td>Bilateral operation. Transient tremor reduction 12/2/6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>68mm/</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>X1.7,Y=-3.7,Z=0.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sin/Lat dors thalamus/</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>12mm/</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>X9.6,Y=-4.1,Z=0.1</td>
<td></td>
</tr>
</tbody>
</table>

* Items 5/6 and 11-14 on the ETRS
Study II

The tremor scores on stimulation were compared to ETRS off stimulation. The total ETRS was reduced by 58.2% (p ≤ 0.001) in the PSA group and by 48.4% (p ≤ 0.001) in the Vim group. This assessment was performed with non-standardized parameters. The Items 5/6 and 11-14 (hand tremor and hand-function) on the treated side improved by 88.3% (p ≤ 0.001) in the PSA group and 56.8% (p ≤ 0.001) in the Vim group.

When the electrode contacts yielding the best results were analyzed with regard to the neuroanatomical area stimulated 54% were found to be located in the Zi/Raprl, 12% in the Vim and the remaining ones in other structures.

When an optimal effect was sought, optimal in this case being arbitrarily defined as improvement in hand function and hand tremor by ≥ 90%, 42.5% of the contacts were located in the PSA and in 17.5% in the Vim. The remaining structures (numbers in brackets) eliciting ≥ 90% improvement were STN (2), Rt (reticular nucleus of the thalamus) (1), Vc (ventrocaudal nucleus) (4), VcPc (ventrocaudal parvocellular) (2), H2 (2), SN (2), Vop (1), Pslp (pes leminsci profundus) (1), Ppd (1), and Lm (medial lemniscus) (2). Some of these structures, such as SN and Lm, appear unlikely to have such a beneficial effect on tremor. This is probably a shortcoming of the Schaltenbrand atlas’ ability to demonstrate individual variations. In 14 electrodes a ≥ 90% improvement was achieved in more than one contact, all of these electrodes being targeted to the PSA.

A ≥ 90% improvement was seen in the average coordinates (in millimeters from the mid-comissural point, MCP) where X = 12.1 ± 1.8, Y = -5.5 ± 1.9, and Z = -1.2 ± 2.9. Only 3.9% of such contacts were seen in the Vim group, all located in the Vim (mean coordinates X = 13 ± 1.4, Y = -1.8 ± 0.5, and Z = 4.1 ± 0.3.) In the PSA group 37 contacts (37%) showed this improvement. The mean coordinates were X = 12 ± 1.8, Y = -5.8 ± 1.6, and Z = -1.7 ± 2.6, and 26 of these contacts were located below the ICL.
Fig 2. Distribution of electrode contacts in Study II. The MCP is marked as origo. (Figure reprinted with kind permission of the publishers.)
Fig. 3. The spatial distribution of the electrode contacts yielding ≥ 90% tremor reduction in Study II. (Figure reproduced with kind permission of the publishers.)
Fig. 4. Topographical contour plots of observed tremor reduction in Study II. The Z value is depicted in each image. White areas correspond to a tremor reduction of > 90%, light gray > 80% tremor reduction. (The figure reproduced with kind permission of the publishers.)
Study III

On average 1.2 tracks were used in order to implant the 31 electrodes. The active contacts were located at coordinates $X = 11.6 \pm 1.8$, $Y = -6.3 \pm 1.6$, and $Z = -3.0 \pm 2.3$. During the introduction of the electrode into the target area, 83% displayed a clear microlesional effect. This effect was persistent even at the follow-up, when the total pre-operative ETRS of $46.2 \pm 10.1$ was decreased to $40.6 \pm 12.7$ (12%) off-stimulation. Total ETRS was on-stimulation further reduced to $18.7 \pm 8.8$ (60%).

Fig 5. Study III. Preoperative MRI fused with a postoperative CT demonstrating the electrode in the left PSA. The image is at the level of the maximal diameter of the nucleus ruber, and the electrode is located 10.9 mm lateral of the midline, 7.7 mm behind the MCP, and 3.5 mm below the ICL. (Image reproduced with kind permission of the publishers.)

In part A (Items 1-9) the improvement was most marked concerning tremor of the contralateral upper extremity (Item 5/6), which showed a reduction of 95% from $6.2 \pm 1.8$ to $0.3 \pm 0.6$. The whole part A improved from $12.9 \pm 4.4$ at baseline to $5.0 \pm 3.0$ (61%) on stimulation. These results were reproduced in the assessment of the contralateral hand function (Items 11-14) where a tremor reduction of 87% from $9.7 \pm 3.6$ to $1.3 \pm 1.5$ was displayed. Part C of the ETRS, activities of daily living (ADL) (Items 15-21), improved from $12.5 \pm 3.5$ before surgery to $4.3 \pm 4.6$ (66%) on stimulation after one year. All these changes were statistically significant ($p \leq 0.001$).
The patients were evaluated five weeks after the surgery. At this stage the mean stimulation parameters were voltage (U) 2.0±0.7 volts (V), frequency, pulse per second (PPS), 163.9 ± 21.8 Hz, and pulse width (PW), 62.7 ± 8.6 microseconds (µs). The pulse effective voltage (PEV) has often been used as a measurement of stimulations strength and it is calculated as √(U² x PPS x PW). In this study the PEV was 0.20 ± 0.09 V. The parameters were relatively constant over the course of time and the PEV at evaluation one year after surgery was U = 2.5 ± 0.8 V, PPS = 165±21 Hz, PW = 61.4 ± 6 µs. Initially, 15 patients (65%) had unipolar stimulation, after one year this number had increased to 78%.

Table 3. ETRS data for Study III. ETRS values at baseline and at follow-up one year after surgery. (The table reproduced with kind permission of the publishers.)

<table>
<thead>
<tr>
<th>Item</th>
<th>Maximum score</th>
<th>Baseline</th>
<th>One year Off</th>
<th>On</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sum ETRS (Items 1-21)</td>
<td>144</td>
<td>46.2±10.1</td>
<td>40.6±12.7</td>
<td>18.7±8.8</td>
</tr>
<tr>
<td>Part A (Item 1-9)</td>
<td>80</td>
<td>12.9±4.4</td>
<td>11.0±4.7</td>
<td>5.0±3.0</td>
</tr>
<tr>
<td>Voice tremor (Item 3)</td>
<td>4</td>
<td>0.3±0.5</td>
<td>0.04±0.2</td>
<td>0.04±0.2</td>
</tr>
<tr>
<td>Head tremor (Item 4)</td>
<td>8</td>
<td>0.4±0.7</td>
<td>0.2±0.5</td>
<td>0.09±0.3</td>
</tr>
<tr>
<td>Tremor of upper extremity (Item 5/6)</td>
<td>12</td>
<td>4.6±2.1</td>
<td>4.8±2.6</td>
<td>4.2±2.4</td>
</tr>
<tr>
<td>Ipsilateral to DBS</td>
<td>12</td>
<td>6.2±1.8</td>
<td>5.3±2.3</td>
<td>0.3±0.6</td>
</tr>
<tr>
<td>Contralateral to DBS</td>
<td>4</td>
<td>0.4±0.7</td>
<td>0.1±0.3</td>
<td>0±0</td>
</tr>
<tr>
<td>Rest</td>
<td>4</td>
<td>2.4±1</td>
<td>1.4±1.1</td>
<td>0.04±0.2</td>
</tr>
<tr>
<td>Postural</td>
<td>4</td>
<td>3.4±1</td>
<td>3.2±0.9</td>
<td>0.2±0.5</td>
</tr>
<tr>
<td>Activity</td>
<td>4</td>
<td>1.5±0.9</td>
<td>1.4±1</td>
<td>0.5±0.6</td>
</tr>
<tr>
<td>Handwriting (Item 10)*</td>
<td>16</td>
<td>18.2±5.5</td>
<td>16.1±6.5</td>
<td>8.8±5.2</td>
</tr>
<tr>
<td>Hand function (Items 11-14)</td>
<td>32</td>
<td>8.1±3.5</td>
<td>8.3±3.9</td>
<td>7.4±4.2</td>
</tr>
<tr>
<td>Ipsilateral to DBS</td>
<td>16</td>
<td>9.7±3.6</td>
<td>7.8±3.5</td>
<td>1.3±1.5</td>
</tr>
<tr>
<td>Contralateral to DBS</td>
<td>16</td>
<td>12.5±3.5</td>
<td>11.8±4.6</td>
<td>4.3±4.6</td>
</tr>
</tbody>
</table>

Values are the means (SD). *Significant vs baseline, p<0.001. +Significant vs baseline, p<0.05. #Significant on vs off stimulation, p<0.001. *n=21. Item 10 is included for all patients in the total ETRS, but the two cases where the patient did not normally use the treated arm for writing have been excluded in this specification of item 10.

Transient mild expressive dysphasia (lasting one to five weeks) occurred in eight patients. Among these patients one had bilateral stimulation, six left-sided and one right-sided DBS. Four of these patients had an additional ipsilateral electrode (one Vim, one PSA, and two STN). No severe complications such as hemorrhages or infections were encountered in this population. In one case a transient mild clumsiness in the contralateral hand and leg was experienced. One patient had a Kinetra IPG with malfunction of some contact. Two patients had revision of the extension cable due to strain in the neck. Transient stimulation induced side effects such as paresthesias, cerebellar signs or blurred vision were frequently encountered when different stimulation settings were evaluated. These side effects were reversible when the stimulation was switched off. In one patient an optimal tremor reduction could not be achieved without...
eliciting blurred vision and dizziness. In this case a lower stimulation current with suboptimal tremor control had to be accepted.

**Study IV**

In the whole material, total ETRS amounted to $49.4 \pm 15.3$ at baseline, and $48.3 \pm 20.4$ off stimulation at the postoperative evaluation (non-significant). On comparing off-stimulation with baseline, the total ETRS scores did not change in the Vim DBS group, while in the PSA DBS group the scores were reduced from $44.7 \pm 12.9$ to $39.1 \pm 18.4$ ($p<0.05$).

Total ETRS on stimulation was $22.4 \pm 14.5$ (a 55% improvement from baseline, $p < 0.001$) in the whole group, $27.5 \pm 16.1$ ($p<0.001$) (49%) in the Vim group, and $17.2 \pm 10.6$ ($p<0.001$) (62%) in the PSA group. On the treated side, hand tremor and hand function (Items 5/6 and 11-14) were reduced by 79% in the whole group and by 70% in Vim and by 89% in the PSA groups, respectively.

**Fig. 5. Relation between age and preoperative level of tremor (A), and between age and postoperative level of tremor (B). The level of tremor is the sum of contralateral Items 5/6(hand tremor) and 11-14 (hand function) from the ETRS. (Reproduced with kind permission of the publishers.)**

In an attempt to establish predicting factors regarding the absolute reduction of tremor after surgery, we tested the following: age at surgery and at postoperative evaluation, duration of disease, gender, and severity of disease (tremor/function of the contralateral hand) as independent factors. The outcome was not correlated with gender, nor was the duration of disease correlated with the severity of tremor or with the degree of postoperative improvement. A statistically significant correlation was found between severity of disease and age ($p = 0.03$). No correlation between reduction of tremor on stimulation, age, relative (percentage) tremor reduction, or the absolute tremor
reduction could be established. The absolute tremor reduction was significantly correlated with the level of tremor preoperatively (p = 0.0001). This correlation was not seen concerning the relative reduction of tremor. Residual tremor after surgery on stimulation was significantly correlated (p = 0.005) with the level of preoperative tremor. Regression analysis showed a predictive value of p < 0.0001. The most important predictive factor was preoperative severity of tremor, while the other factors were of limited predictive importance.

Fig. 6. Relation between preoperative level of tremor and postoperative reduction of tremor in absolute terms (A), between preoperative level of tremor and postoperative relative reduction of tremor (B), and between preoperative level of tremor and postoperative residual tremor on stimulation (C). The level of tremor is the sum of contralateral Items 5/6 (hand tremor) and 11-14 (hand function) from the ETRS. (Reproduced with kind permission of the publisher.)
Table 4. Pre- and postoperative ETRS-data for Study IV. (Table modified from Blomstedt et al with kind permission of the publishers.229).

<table>
<thead>
<tr>
<th>Item</th>
<th>PSA</th>
<th>Vim</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Max score</td>
<td>Base line</td>
</tr>
<tr>
<td></td>
<td>Off</td>
<td>On</td>
</tr>
<tr>
<td><strong>Sum ETRS (Items 1-21)</strong></td>
<td>144</td>
<td>44.7±12.9</td>
</tr>
<tr>
<td><strong>Part A (Items 1-9)</strong></td>
<td>80</td>
<td>12.6±5.1</td>
</tr>
<tr>
<td><strong>Voice tremor (Item 3)</strong></td>
<td>4</td>
<td>0.5±1.1</td>
</tr>
<tr>
<td><strong>Head tremor (Item 4)</strong></td>
<td>8</td>
<td>0.6±1.3</td>
</tr>
<tr>
<td><strong>Tremor of upper extremity (Item 5/6)</strong></td>
<td>12</td>
<td>4.1±2.4</td>
</tr>
<tr>
<td><strong>-ipsilat to DBS</strong></td>
<td>12</td>
<td>6.2±1.8</td>
</tr>
<tr>
<td><strong>-contralat to DBS</strong></td>
<td>4</td>
<td>0.5±0.8</td>
</tr>
<tr>
<td><strong>--rest</strong></td>
<td>4</td>
<td>2.4±0.9</td>
</tr>
<tr>
<td><strong>--postural</strong></td>
<td>4</td>
<td>3.2±1.0</td>
</tr>
<tr>
<td><strong>Handwriting (Item 10)</strong></td>
<td>4</td>
<td>1.4±1.2</td>
</tr>
<tr>
<td><strong>Hand function (Items 11-14)</strong></td>
<td>32</td>
<td>17.8±6.3</td>
</tr>
<tr>
<td><strong>-ipsilat to DBS</strong></td>
<td>16</td>
<td>8.0±3.6</td>
</tr>
<tr>
<td><strong>-contralat to DBS</strong></td>
<td>16</td>
<td>9.5±4.0</td>
</tr>
<tr>
<td><strong>ADL</strong></td>
<td>28</td>
<td>12.4±3.7</td>
</tr>
</tbody>
</table>
Study V

The total ETRS decreased from 48.1 ± 12.6 before surgery to 18.8 ± 10.9 (61%) on stimulation. Hand tremor (Item 5/6) in the treated hand was reduced by 95% (6.3 ± 2.3 to 0.4 ± 0.6) and hand function (Items 11-14) was improved by 78% (9.9 ± 3.7 to 2.1 ± 2.2). Handwriting (Item 10) improved by 69% (from 1.3 ± 1 to 0.5 ± 0.7). The ADL score of the ETRS (Items 15-21) improved by 71% (13.4 ± 3.7 to 3.9 ± 4.1). All these analyses rendered a p-value of <0.05.

<table>
<thead>
<tr>
<th></th>
<th>Before surgery</th>
<th>After surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total ETRS</td>
<td>48.1 ± 12.6</td>
<td>18.8 ± 10.9*</td>
</tr>
<tr>
<td>ETRS Item 5/6 (hand tremor for treated hand)</td>
<td>6.3 ± 2.3</td>
<td>0.4 ± 0.6*</td>
</tr>
<tr>
<td>ETRS Item 10 (hand writing)</td>
<td>1.3 ± 1.0</td>
<td>0.5 ± 0.7*</td>
</tr>
<tr>
<td>ETRS Items 11-14 (hand function for treated hand)</td>
<td>9.9 ± 3.7</td>
<td>2.1 ± 2.2*</td>
</tr>
<tr>
<td>ETRS Items 15-21 (ADL)</td>
<td>13.4 ± 3.7</td>
<td>3.9 ± 4.1*</td>
</tr>
<tr>
<td>SF-36 MCS</td>
<td>44.9 ± 10.2</td>
<td>48.7 ± 11.7</td>
</tr>
<tr>
<td>SF-36 PCS</td>
<td>47.3 ± 10.3</td>
<td>44.8 ± 10.7</td>
</tr>
<tr>
<td>QUEST-SI</td>
<td>0.31 ± 0.2</td>
<td>0.2 ± 0.2*</td>
</tr>
<tr>
<td>QUEST ADL</td>
<td>60.4 ± 20.2</td>
<td>36.1 ± 28.9*</td>
</tr>
<tr>
<td>QUEST psychosocial</td>
<td>35.2 ± 15.7</td>
<td>20.8 ± 20.6*</td>
</tr>
<tr>
<td>QUEST communication</td>
<td>17.2 ± 20.5</td>
<td>12.5 ± 18.9</td>
</tr>
<tr>
<td>QUEST hobbies/leisure</td>
<td>32.3 ± 22.3</td>
<td>23.4 ± 27.3</td>
</tr>
<tr>
<td>QUEST work/finance</td>
<td>21.9 ± 25.8</td>
<td>13.0±21.0</td>
</tr>
</tbody>
</table>

On assessing the QoL the changes were not equally clearly visible. The QUEST questionnaire showed a statistically significant improvement in the ADL (40%) and psychosocial (41%) subscores (p = 0.004 and 0.02,
respectively.) The QUEST-SI also showed significant improved (33%, \( p = 0.02 \)). No statistically significant changes were seen regarding the SF-36. (Table 5).
Discussion

“As we know, there are known knowns; there are things we know we know. We also know, there are known unknowns, that is to say, we know there are some things we do not know. But there are also unknown unknowns, the ones we do not know.”

Donald Rumsfeld, Department of Defense news briefing, February 12 2002

PSA DBS in ET

ET is a common disease and discoveries during the past 20 years have led to a better understanding of the clinical symptoms, the abnormalities of the motor system, and the behavioural consequences of this condition. Forty years ago Bertrand described a target in the PSA as the optimal target for the treatment of tremor.\textsuperscript{102} Several studies have shown excellent results of DBS in the PSA.

A good outcome after cZi DBS was confirmed by the results in Studies III, IV and V. In Study III the total ETRS score was reduced by 60% on comparing baseline to the on stimulation evaluation one year after surgery. Hand tremor and hand function improved by 95% and 87%. The ADL part of the ETRS improved by 66%. The results from this study, as well as the those from Studies IV and V, are consistent with what has been reported by other groups targeting PSA, Raprl and Zi/cZi.\textsuperscript{151,152,167,184,192,230} The microtomy “setzeffect” has often been described as a characteristic of the PSA area and it was seen in 83% of our patients in Study III.\textsuperscript{98,101,104,120,167,231,232}

Complications after PSA DBS are of interest, since it has been suggested that subthalamotomies were abandoned in favour of thalamotomies, due to the complications encountered with the former procedure.\textsuperscript{167,192} Complications after PSA DBS have in general, however, been few, mild and transient, and regarding ET only reversible stimulation-induced side effects have been reported.\textsuperscript{151,152,167,192} No severe or permanent complications in connection to DBS were seen in our studies.

In Study I one third of the patients reported a mild transient dysphasia after the operation. The dysphasia was always mild, and in some cases noticeable only to the patient and not to the investigator. It was related to the surgical intervention and occurred before the initiation of the chronic stimulation. We are unsure as to whether the dysphasia was caused by the intervention in the cZi/PSA or by traversing the thalamus. In thalamotomies dysphasia has been reported to occur frequently, especially in the procedures in the dominant hemisphere.\textsuperscript{233-239}
It would seem that, when plotted onto the Schaltenbrand atlas, the active contacts presented in Study III correspond to Raprl. The calculation of active contacts in Study III is based on a mean value, which in itself is of limited interest. In reality, the active contacts are dispersed in both the Zi and Raprl and the spread of the current is likely to affect even more substructures. This observation has also been made in Study II. Because of the proximity of the substructures, a patient might have contacts in inferior parts of Vim as well as Zi and Raprl.

The interpretation of the position of the contacts is based on their relationship to the AC and PC as demonstrated in the Schaltenbrand stereotactic atlas. Unfortunately the commissures and their relationship to the basal ganglia have been reported to have a rather high degree of individual variability. Because of this it is difficult to exactly state which substructure contributes to the beneficial effects. This also makes evaluation of the stimulated substructure difficult.

The results from Studies II and III give the impression that cZi DBS seems to compare favorably with Vim DBS. Vim DBS is an established treatment and there are many publications proving its beneficial effects. Unfortunately, it is difficult to make direct comparisons between our results pertaining to PSA DBS and those of studies on Vim DBS. Even though the reports are normally based on the ETRS, the selection, grouping, and presentation of the different items vary highly. Differences in follow-up time makes comparisons hazardous, and frequent mixing of unilateral and bilateral procedures into the same group adds to the confusion.

In Study IV PSA DBS yielded an improvement of 89% when the tremor in the treated hand was assessed. Vim DBS gave improvement of 70%. The two groups were similar with regard to age, gender distribution, and size. However the follow-up was conducted one year after surgery in the PSA group and after a mean of 28 months in the Vim group. This might be a disadvantage for the Vim group, especially since tolerance development is a well-known problem after Vim DBS. Furthermore it is necessary to take into account the actual location of the electrode contact as discussed below.

**The Optimal Target**

It is interesting to note that a number of studies evaluating the electrode position in Vim DBS have found that the best effect is often achieved, not within the thalamus, but in the PSA. Since the Vim is located dorsally to the PSA, simply by advancing an electrode aimed for the Vim, the PSA is usually reached. This is in line with our collected experience of Vim DBS where optimal intraoperative macrostimulation has resulted in a better response in some patients a few millimeters deeper and hence resulted in a PSA DBS later confirmed on imaging. This is consistent with several studies reporting a good effect of DBS in PSA/cZi.
Even though the older material concerning the localization of lesions in the PSA is quite abundant, this is not true concerning DBS in the PSA.\textsuperscript{102,128} The target within the PSA does, however, vary somewhat between different groups, and some have specifically targeted different substructures in the PSA, i.e. the Z/cZi and Raprl.\textsuperscript{152,167,255} Only in a few studies are the coordinates of the contacts used reported, and these are of course not always identical with the coordinates of the targeted point.\textsuperscript{167,170,256,257}

Plaha et al. state the optimal stimulation target to be in the cZi, Velasco et al. place it in the Raprl and both Kitagawa and Murata as well as our group place the target somewhere in between.\textsuperscript{128,152,167,227} Plaha et al. place the target posterior-medial to the posterior-dorsal STN.\textsuperscript{170,258} Not many studies have attempted to link the outcome of the surgery to the location of the electrode.\textsuperscript{19,242,252-254} Some recent studies have identified the target in relation to the STN and nucleus ruber.\textsuperscript{152,167,170,256,258}

The contour plot in Study II was an attempt to delineate areas that yielded over 90\% tremor reduction in the treated arm. In the plot we have found two separate areas giving optimal tremor reduction. Both plotting the coordinates of this area onto the Schaltenbrand atlas and examining the radiological studies would seem make these regions compatible with Zi and Raprl.

The literature is rather consistent concerning the statistical coordinates for the target in the PSA. According to Bertrand and Velasco, the target, Raprl, is identified by dividing the ICL into 10 equal segments.\textsuperscript{102} The target will then be located 8/10 behind AC, 5/10 lateral to the midline and 1-2/10 below the ICL. If the ICL is 25 mm, the optimal target will be located 12.5 mm lateral to the MCP, 20 mm behind the AC and 2.5 - 5.0 mm below the ICL.\textsuperscript{185,255} This is rather representative of the literature, which most frequently places the target at $X = 10 - 14$, $Y = -4.5 - -7.5$ and $Z = -2 - -4$.\textsuperscript{170,257,167,252,254,256} These correspond well to the results from Study II, where the contacts yielding the best results were located in $X = 12 \pm 1.8$, $Y = -5.8 \pm 1.6$, and $Z = -1.7 \pm 2.6$. On comparing different research groups, there appears to be a slight variation of the target in Vim, but frequently stated coordinates are $X = 11.5 - 15$, $Y = -5$, and $Z = 0$.\textsuperscript{242}

The target should not be assumed to be a certain point but rather a continuum of different substructures that are being affected by the stimulation. Unfortunately it is not known exactly how the different substructures such as Zi, Raprl, fields of Forel, and cerebellothalamic fibers exactly contribute to the tremor suppressing effect. A recent study fusing diffusion tensor image fiber tracking with postoperative CT has suggested that the cerebellothalamic fibers in the cZi contribute to a significant tremor reduction.\textsuperscript{150}

Study II makes an attempt at identifying the location that yields the best response for tremor. In this study more patients whose stimulation was intended for Vim actually did attain a better effect in the PSA than in Vim when contralateral distal hand tremor was evaluated. The two groups of Vim and PSA stimulation should not be considered directly comparable because of the time to
follow-up. The PSA group was followed up one year after surgery, whereas the Vim group was followed up 66 ± 38 months after surgery. This increases the likelihood of tolerance development and progression of the disease in the Vim group.\textsuperscript{189}

In the PSA group the number of contacts yielding a tremor reduction over 90\% was ten times higher than in the Vim group. In the Vim group more patients had more tremor reduction with contacts located in the PSA than with the contacts located in the Vim. However, the effect of stimulation in the PSA in the Vim group was not as good as the effect of stimulation in the PSA in the PSA group. We think this might be because the Vim electrodes in the PSA are electrodes that have unintentionally crossed down to the PSA while doing the final adjustment according to macrostimulation. When aiming for the PSA one is probably more likely to attain a more optimal position in the PSA.

Study II has a clear limitation in the identification of different substructures. This could probably explain to some extent why such a wide variety of substructures yielded excellent tremor reduction in Study II. The Schaltenbrand atlas does not adequately enough identify the interindividual variations. This is evident in the case of the patient in whom, according to the atlas, the contacts were in the STN, whereas examination of the MRI images revealed the electrode to be located in the Zi. Also noteworthy is that the substructure differed slightly when the coronal and sagittal images in Schaltenbrand were examined. In this study the transaxial images were applied.

The conclusion from Study II would be that we define the optimal stimulation area as a target that maximizes the likelihood of a good effect from stimulation of any of the four contacts including the most rostral in the thalamus.

**PSA DBS and Quality of Life**

ET is a not a monosymptomatic movement disorder but rather a more complex condition with tremor and other non-tremor symptoms such as a moderate cognitive deficit, higher risk of depression, distinct personality characteristics and other affective symptoms.\textsuperscript{14} Compared to a healthy age-matched population, patients with ET are known to have a lower QoL, especially in aspects related to psychosocial functioning.\textsuperscript{27,31,32} The tremor often causes impairment in ADL functioning and a poorer QoL especially in aspects related to psychosocial functioning.\textsuperscript{14,27,31,42} The psychosocial impairment is considered to be caused by the affection of mood and the predisposition to depressions.\textsuperscript{14} The subjective perception of the impairment, coping skills and disease recognition also display a significant interindividual variation.\textsuperscript{39}

It is complicated to evaluate the QoL and disability in this condition. Several factors such as age, anxiety, and depression have been shown to be linked to a greater perception of disability in ET than the tremor itself.\textsuperscript{27} This might suggest
that the PCS of SF-36 reflects general mobility rather than disability and symptoms typical for ET.

All these factors make it clear that analyzing the tremor component is not sufficient when evaluating a treatment for ET. QUEST is a scale that has been developed exclusively for ET, but unfortunately it has not gained much use as a clinical tool in studies. SF-36 is an established and much used scale, but it tends to be so general that the specific symptoms of ET might have a limited impact on the PCS of the SF-36. The impaired QoL is clearly stated by the MCS in the SF-36 scale. Lorenz et al. demonstrated in a study that the MCS in ET patients over 40 years of age is below the 20th percentile compared to healthy controls. This is in contrast to the PCS, which is often close to what the age-adjusted normal population displays.

In Study V we achieved a good result on tremor in the treated hand as well as on the ADL subscore (Part C) of the ETRS. The improvement seen in QUEST was modest and in SF-36, non significant. The effect of Vim DBS on tremor has been documented in a substantial amount of scientific studies but the effects on QoL and ADL have been addressed in a much smaller number of studies. All of these studies have indicated improvements in QoL and ADL. Improvements in ADL have also been shown to be highly correlated with patient satisfaction. This has also been reflected by a study evaluating outcome goals that the patients themselves have set before surgery. Many of these goals consisted of common everyday tasks such as eating, writing and hygiene routines.

The number of studies on QoL after cZi DBS is limited, to our knowledge, to only one study by Plaha et al. This study presents 15 patients with bilateral cZi DBS with statistically significant improvement in MCS and PCS on the SF-36. Although the effect on tremor appears to have been excellent, the improvement in QoL was only modest. However, the improvement in QoL that Plaha et al. describe is better than the marginal and insignificant effects in our own series. It seems likely that this difference could be partly explained by the fact that only two of our 16 patients had bilateral surgery. The residual tremor in the nontreated hand might affect the overall QoL. Although here it has to be kept in mind here that the 74 % improvement in ADL in Study V has to be considered to reflect the patients perception of everyday life and has to be deemed as good. The improvement in QoL evaluated by QUEST was 33%, a significant improvement. But, as previously stated, QUEST has not been used as a primary outcome measure in clinical trials and this makes this improvement in Study V difficult to interpret.

It might be that the lack of compatibility between the improvement in tremor and ADL and improvements in QoL show that there is no strict correlation between the motor symptoms of ET and QoL. SF-36 is a good tool for measuring differences between a healthy population and a population with a disease, but probably a poor tool for analyzing changes in an affected population over a limited time. It seems unlikely that factors such as social isolation would change dramatically over the course of a year, despite successful
surgery. ET is a complex condition in which ETRS, ADL and QoL need to be taken into account when evaluating a treatment. Further studies on how to interpret QoL in ET are needed.

**Prognostic Factors**

ET is a progressive disease in which increased symptoms are seen with increasing age. In the population over 60 years of age the prevalence is estimated to be around 6%. Although there are no publications to support it, our impression has been that older patients get a worse outcome from DBS surgery. This could not be demonstrated in Study IV. There was no correlation between the outcome of the treatment and the patients’ age. It might be of interest to note that older patients tend to have more severe tremor before surgery and this might partly explain our previous assumption. It is further probable that the older patients might be more vulnerable to various complications and side effects, which might decrease the overall benefit of the surgery. This aspect has not been evaluated in this material.

We have also been under the impression that the severity of disease affects the outcome after DBS surgery. This could be considered both right and wrong. There was no correlation between the severity of disease and the percentage tremor reduction. The more severe tremor the patient has before surgery, the more residual tremor he will have after surgery on stimulation.

In Study IV neither the preoperative status nor the outcome after surgery showed any gender-related differences. In this study the number of females did, however, constitute less than one third of the patients operated on. ET is not known to show differences in prevalence between males and females. A recent study report ET to have a slight male predominance of 1.08:1. This ratio is not sufficient to explain the large male predominance in our material. It is possible that the reason for this should be sought in gender-related differences in the patients’ perception of their symptoms, their attitude towards surgery and the attitude of the physicians. Study IV can only conclude that DBS for ET is as efficient in females as in males.

Together with the different follow-up periods between Vim DBS and PSA DBS groups, and the non-randomized nature of Study IV there are some clear limitations. It is not possible to directly compare the two groups.

**Thalamotomies**

DBS has been an established treatment for many years but it is also linked to many problems. High cost, hardware-related complications, infection risk, life-long follow-up, and a somewhat declining effect over time have been issues when the use of lesional procedures as an alternative to DBS has been discussed. The concept of lesioning is based on a minimal tissue destruction being elicited within the most appropriate site providing maximal
benefit without side effects. The first cases of thalamotomy for ET were described in the 1960s by Guiot. He was followed by Cooper and Laitinen who reported successful surgical treatment of ET. In the late 1960s three studies described good results in altogether 47 of 50 patients. Several studies have shown positive effects in long-term evaluations after thalamotomies. Ohye et al. reported in 1982 complete and near-complete abolition of tremor in 15 subjects. In the late 1960s three studies described good results in altogether 47 of 50 patients. Ohye et al. reported in 1982 complete and near-complete abolition of tremor in 15 subjects.

In Study I all patients experiencing tremor alleviation had recurrence of tremor. The longest duration of tremor relief experienced was 20 years, the shortest just a few years. The ETRS scores seen at the follow-up were at about the same level as seen in our current patients during the preoperative assessment. This might suggest some extent of a lasting effect since it could be assumed that the patients had a more severe tremor in the treated hand at baseline.

The rate of persistent severe complications after thalamotomy has been reported in the literature to range from 9-28%. Cerebellar complications such as dysarthria, disequilibrium, apraxia, ataxia, and gait disturbance, often irreversible, have been described. All the above-mentioned side effects, as well as contralateral weakness, most probably due to affection of the internal capsule, have been described in thalamotomies for ET as well as other movement disorders. Other side effects listed are general speech difficulties, facial numbness or weakness, cognitive impairment and hypophonia (in bilateral lesions).

To the best of our knowledge there are only a few studies that attempt to relate effects and side effects to the location and size of the lesion. Studies suggest the effective lesion to be approximately 40-70mm3. There appears to be a large variation in lesion size, and Hariz et al. have reported larger lesions to be linked to more complications. The same study reports that 15.7% of lesions were impossible to visualize, all of these cases had different outcomes. Some data suggest no correlation between location in the ventrolateral thalamus, lesion size and tremor reduction.

In our limited study population in Study I no correlation between lesion size and ETRS could be seen. The average number of coagulations per lesion was 2.1, which is quite consistent with the numbers reported by other groups. A wide distribution of lesions locations was seen in our population and no correlation between location and tremor relief could be established. The mean coordinates were slightly more posterior and superior compared to the lesion target presented by Hariz et al. in previous publications from our department. The coordinates quoted in their study are 6-7mm in front of the posterior commissure at the level of the ICL and 13-15mm lateral to the midline of the third ventricle. Four patients had lesions we assumed to affect the internal capsule and all of them showed contralateral motor impairment. One patient had an exceptionally large lesion (68 mm3), which might be due to the field potential recording used during that particular surgery.
Impaired balance control and motor speech are typical findings in ET, even in early stages. This has been attributed to the cerebellar impairment in ET and makes the evaluation of balance difficult. Normal gait is usually unaffected but tandem movement tends to be the most affected. When we assessed the balance using BBS in Study I, no impairment could be found. Eight out of nine patients exhibited an abnormal tandem walking which should probably be interpreted as a manifestation of the disease rather than as a side effect of the lesion.

Some studies have suggested that thalamotomy might interfere with cognitive functioning. The laterality has also been shown to influence neuropsychological outcome, with greater impairment after left sided surgery. Our population in Study I had an even distribution of laterality of lesion and no correlation of side or cognitive effect could be established.

Both transient and persistent speech difficulties, as well as facial weakness and numbness, have been described after thalamotomies. Bilateral surgery increases the risk of dysarthria as well as hypophonia. In our series the only patient with bilateral lesions experienced dysarthria but no hypophonia. This dysarthria could not be verified by a speech pathologist. One third of the patients experienced impaired speech after surgery, but no consistent pattern of speech pathology could be established.

As previously mentioned, patients with ET are known to have a lower QoL, especially in aspects related to psychosocial functioning. Unfortunately there are not many studies that rate the QoL after lesional procedures, and to our knowledge there is only one recent study using SF-36 as a follow-up tool for assessing QoL after stereotactic surgery. In this study Plaha et al. have evaluated patients with DBS in the cZi 84 months after surgery. In this group the SF-36 PCS after surgery was 55.5 ± 6.3 compared to 38.2 ± 9.7 in our series. The MCS showed a similar trend, Plaha’s group displaying an MCS of 60.1 ± 6.2 compared to our 38.2 ± 9.7.

Although DBS is an attractive alternative to lesioning for a variety of reasons, lesions remain a viable strategy, especially in underdeveloped countries where the economic and technological infrastructure is limited. It might be an important distinction that DBS allows bilateral procedures without the high incidence of side effects associated with ablative procedures. It is possible that thalamotomies might be considered a safe and efficient alternative in cases where expenses or infection risk might be limiting factors. This is provided that improvements in safety, lesioning and targeting have been made.
Conclusions

DBS in the cZi/PSA has in these studies proven to be highly effective in the treatment of ET and compares favourably with results from Vim DBS.

The results from this thesis would suggest that cZi is a preferential target to Vim.

In the Vim DBS population in this thesis the best contacts were located in the PSA.

The optimal contact location appears to be in the PSA/cZi, with the most cranial contact in the rostral Vim.

The improvement in ADL after surgery is good but the improvements on the QoL scores are more modest. New ways to evaluate QoL after surgery for ET might be needed.

No correlation between the outcome of DBS for ET and gender or age could be established. The preoperative severity of tremor is the most important factor regarding outcome.

The benefits of thalamotomies were few in quantity and the complications were frequent. No correlation between lesion location within thalamus, lesion size and long-term outcome could be established.
Acknowledgements

I wish to express my deep gratitude to my co-authors and to all those who have been involved in these studies and have supported me in my work. I would especially like to thank:

Associate Professor Patric Blomstedt, my friend and supervisor, without whom none of this would have been possible. Thank you for all your support, refreshing ideas, laughter and an incessant supply of espresso.

Associate Professor Lars-Owe Koskinen my co-supervisor for valuable advice and help with the statistics.

Professor Marwan Hariz, for conversations that clarified my thinking about stereotactic functional neurosurgery. Thank you for always being helpful and ever since day one making me feel like an active member of the academic community.

Professor Tommy Bergenheim, for all the professional and musical advice.

Dr. Gun-Marie Hariz, for sharing your knowledge of function, quality of life and other esoteric values not measurable with biological or radiological parameters.

Dr. Jan Linder, for always patiently answering my questions and teaching me more about movement disorders.

Professor Jan van Doorn and the Division of Speech and Language Pathology for help with Study I.

Anna Fredricks, our skilful DBS specialist nurse, for patiently helping me out with charts and ratings scales.

Gull-Britt Widefjäll and Kerstin Gruffman, for administrative help.

My dear friends and colleagues, Maria Eriksson and Lukas Bobinski for friendship, laughter, and immense amounts of chocolate.

My dear friend Maja Hansson for proofreading, wine and good company.

My dear friends, Elin Söderberg Hedman, Ingela Nygren and Erika Rasmuson, for forcing me to relax every Wednesday evening.

My colleagues at the Neurosurgical Department.

My family, my parents, Elisa and Jan Sandvik, my sister Laura Eyvindson, and my brother-in-law, Kyle Eyvindson, for believing in me.

My dear husband, Raimond Gren, fide et amore, thank you for your love and support in every way possible.
"Lose this day loitering - 'twill be the same story
To-morrow - and the next more dilatory;
Each indecision brings its own delays,
And days are lost lamenting o'er lost days,

Are you in earnest? Sieze this very minute -
Boldness has genius, power and magic in it.
Only engage, and then the mind grows heated -
Begin it, and then the work will be completed!"

Johann Wolfgang von Goethe, Faust, 1808
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