Deep brain stimulation targeting the caudal Zona incerta as a treatment for Parkinsonian and Essential tremor

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This work is dedicated to Marina
It is a rule that easy reading is hard writing, and to construct anything that the mind takes in without effort, and without being puzzled by it, is a triumph of art

Charles Allston Collins, 1860
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Abstract

Background: Deep brain stimulation (DBS) is used as a treatment for Parkinson’s disease (PD) and Essential tremor (ET) when medications are insufficient. The most common DBS-targets for PD and ET, the subthalamic nucleus (STN) and the ventral intermediate nucleus of the thalamus (Vim) respectively, have certain side effects and limitations. In the early 2000s, the posterior subthalamic area (PSA) was introduced as an alternative DBS-target with good results on PD and ET in non-blinded, non-randomised, short-term studies. Different structures in the PSA, such as the caudal zona incerta (cZi), have been used as targets but an optimal target within this area has not been established. Furthermore, there has been an increased interest in asleep DBS surgery but with a paucity of results of asleep surgery for ET, as the Vim is not visible on conventional MRI.

Aims: To evaluate DBS targeting the cZi for PD in a blinded, randomised manner. To spatially map the effects of DBS within the PSA. To evaluate the long-term effects of cZi-DBS on PD tremor and ET. To analyse the outcome of awake and asleep cZi-DBS surgery for ET.

Method: The thesis is based on five studies. Bilateral cZi-DBS was compared to Best Medical Treatment for PD in a randomised blinded trial. The long-term effects of unilateral cZi-DBS on PD tremor were evaluated retrospectively. Prospectively collected data on cZi-DBS for ET were used to evaluate long-term effects and compare awake and asleep surgery. The effects of cZi-DBS were spatially mapped within the PSA using electric field simulations and contact location in relation to the STN.

Results: Bilateral cZi-DBS improved motor symptoms and quality of life in patients with PD in both blinded and non-blinded evaluations with a pronounced effect on tremor (90%) and a modest on bradykinesia (25-40%). The effects of unilateral cZi-DBS on PD tremor remained undiminished at a mean of five years after surgery. cZi-DBS significantly improved ET 10 years after surgery with a slight deterioration over time. Asleep surgery had similar effects and side effects as awake surgery for patients with ET. Electric field simulations did not reveal an optimal target but together with contact location analyses consistently found that the stimulation was concentrated within the PSA, overlapping the cZi and the cerebellothalamic tract.

Conclusion: DBS targeting the cZi reliably achieved a pronounced effect on PD tremor and ET up to at least five and ten years after surgery respectively. In addition, cZi-DBS had a modest effect on bradykinesia and improved quality of life in patients with PD. Finally, targeting the cZi enabled asleep surgery with seemingly similar efficacy as awake surgery for ET.
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>ADL</td>
<td>Activities of Daily Living</td>
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<td>BMT</td>
<td>Best Medical Treatment</td>
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<td>DBS</td>
<td>Deep Brain Stimulation</td>
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<td>ET</td>
<td>Essential Tremor</td>
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<td>ETRS</td>
<td>Essential Tremor Rating Scale</td>
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<td>FEM</td>
<td>Finite Element Method</td>
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<tr>
<td>Hz</td>
<td>Hertz</td>
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<tr>
<td>IPG</td>
<td>Implantable Pulse Generator</td>
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<td>LEDD</td>
<td>Levodopa Equivalent Daily Dosage</td>
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<td>LFP</td>
<td>Local Field Potential</td>
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<td>MCP</td>
<td>Midcommissural Point</td>
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<td>MER</td>
<td>Microelectrode Recording</td>
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<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<td>PD</td>
<td>Parkinson’s Disease</td>
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<td>PDQ</td>
<td>Parkinson’s Disease Questionnaire</td>
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<tr>
<td>PEV</td>
<td>Pulse Effective Voltage</td>
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<td>PSM</td>
<td>Probabilistic Stimulation Map</td>
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<tr>
<td>Pw</td>
<td>Pulse width (µs, microseconds)</td>
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<tr>
<td>QoL</td>
<td>Quality of Life</td>
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<tr>
<td>UPDRS</td>
<td>Unified Parkinson's Disease Rating Scale</td>
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<tr>
<td>V</td>
<td>Volt</td>
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<tr>
<td>VNA</td>
<td>Volume of Neural Activation</td>
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Anatomical Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>Al</td>
<td>Ansa lenticularis</td>
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<tr>
<td>AC/PC</td>
<td>Anterior/Posterior Commissure</td>
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<tr>
<td>cZi</td>
<td>caudal Zona incerta</td>
</tr>
<tr>
<td>DRTT/CTT</td>
<td>Dentato-rubro-thalamic/Cerebellothalamic Tract</td>
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<tr>
<td>Fct</td>
<td>Fasciculus cerebellothalamicus</td>
</tr>
<tr>
<td>Fl</td>
<td>Fasciculus lenticularis</td>
</tr>
<tr>
<td>Ft</td>
<td>Fasciculus thalamicus</td>
</tr>
<tr>
<td>GPi/e</td>
<td>Globus Pallidus interna/externa</td>
</tr>
<tr>
<td>H/H1/H2</td>
<td>Fields of Forel</td>
</tr>
<tr>
<td>PSA</td>
<td>Posterior Subthalamic Area</td>
</tr>
<tr>
<td>PTT</td>
<td>Pallidothalamic Tract</td>
</tr>
<tr>
<td>Raprl</td>
<td>Radiatio prelimniscalis (Prelemniscal radiations)</td>
</tr>
<tr>
<td>RN</td>
<td>Red Nucleus</td>
</tr>
<tr>
<td>SNc/r</td>
<td>Substantia Nigra pars compacta/reticularis</td>
</tr>
<tr>
<td>STN</td>
<td>Subthalamic Nucleus</td>
</tr>
<tr>
<td>Vim</td>
<td>Ventral intermediate nucleus of the thalamus</td>
</tr>
<tr>
<td>VL/VLp/VLa</td>
<td>Ventral Lateral posterior/anterior thalamus</td>
</tr>
<tr>
<td>Vop/Voa</td>
<td>Ventral oral posterior/anterior thalamus</td>
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Sammanfattning på svenska

Parkinsons sjukdom (PS) och Essentiell tremor (ET) är två sjukdomar som båda ger upphov till ofrivilliga skakningar (tremor). PS ger även upphov till små och förlångsamma rörelser (bradykinesi) och muskelstelhet (rigiditet). Dessa symtom har en negativ inverkan på funktionsförmågan och livskvaliteten hos personer med dessa sjukdomar. Dagens behandlingar av PS och ET fokuserar på symtomlindring, oftast med läkemedel. De personer med otillräcklig effekt eller besvärliga biverkningar av läkemedel kan vara hjälpta av hjärnkirurgi i form av djup hjärrnjstimulering, så kallad Deep Brain Stimulation på engelska (DBS).


Denna avhandling utvärderar ett alternativt målområde för DBS, en struktur som heter zona incerta (cZi). En fördel med cZi är att det går att bekräfta ett gott elektrod läge med hjälp av röntgen och MR vilket möjliggör kirurgi i narkos. cZi-DBS har visat sig lindra symtomen vid PS och ET i flera studier. Dessa studier har dock genomförts med icke blindade utvärderingar, utan kontrollgrupp och med relativt kort uppföljning, vilket begränsar den vetenskapliga styrkan av resultaten i dessa studier.

Mål: Syftet med denna avhandling var att utvärdera effekten av cZi-DBS vid PS och ET, bland annat med blindad utvärdering. Vidare ville vi utvärdera långtidseffekterna av cZi-DBS för både PS och ET. Vi ville även utvärdera om det fanns någon skillnad i utfall mellan patienter som genomgick DBS-kirurgi i narkos jämfört med vaken kirurgi för ET. Slutligen ville vi kartlägga effekten av stimuleringen i förhållande till anatomin.

Metod: Avhandlingen är baserad på fem studier. Studie I var en klinisk prövningsstudie där patienter med PS som var lämpliga för DBS slumpades till antingen cZi-DBS eller bästa medicinska behandling med kontinuerlig läkemedelsjustering. Dessa grupper utvärderades blindat efter sex
månader. De patienter som slumpats till läkemedelsjustering erbjöds därefter operation.

Studie II är 1-årsuppföljningen av cZi-DBS hos patienter från första studien. Studie III analyserar retrospektivt utfall hos patienter som har haft cZi-DBS för PS-tremor längre än 3 år. För att kartlägga effekten av DBS i förhållande till anatomin gjordes även simuleringar av det elektriska fältet runt elektroderna i studie II och III. Studie IV använder sig av prospektivt insamlade data för att analysera utfall hos patienter som behandlats med cZi-DBS för ET i 10 år. Studie V använder data från samma kohort som studie IV för att undersöka skillnader i utfall mellan vaken och sövd DBS-kirurgi för ET.

**Resultat:** Studie I och II visade att cZi-DBS lindrade symtom och förbättrade livskvaliteten hos patienter med PS. cZi-DBS minskade armtremor med 88–90% och bradykinesi med 25–40%. Studie III visade att effekten på PS-tremor var oförändrad upp till fem år efter operationen. Simuleringar av de elektriska fälten runt elektroderna visade i studie II och III att effekten av cZi-DBS uppnås framför allt av stimulering i ett område som inkluderar såväl cZi som nervbanor från lillhjärnan till talamus.

Studie IV och V visade att cZi-DBS förbättrade armtremor och handfunktion med 83% vid ET. cZi-DBS gav signifikant symtomlindring även 10 år efter operationen, med lätt försämrad effekt över tid. Studie V visade liknande förbättring hos patienter som genomgått vaken kirurgi som de patienter som genomgått kirurgi i narkos. En ensidig operation var i snitt 1 timme och 39 minuter kortare om den genomfördes i narkos jämfört med vaken. Kartläggning av stimuleringen visade att patienter som genomgått sövd kirurgi använde mindre ström och stimulerade något ytligare i målområdet än patienter som genomgått vaken kirurgi.

**Slutsats:** DBS med cZi som mål ger en påtaglig lindring av tremor vid PS och ET, ger viss lindring av bradykinesi samt verkar förbättra livskvaliteten hos patienter med PS. Tremor lindras upp till 5 och 10 år efter operationen för PS respektive ET, med en något minskad effekt över tid gällande ET. Stimuleringen verkar täcka ett område omfattande såväl zona incerta som nervbanor från lillhjärnan till talamus. Dessa nervbanor är centrala delar av nätverk där störningar i signalmönster är associerat med tremor, både vid PS och ET. Genom att använda cZi som mål möjliggjordes kirurgi i narkos, till synes utan påtaglig skillnad i effekt jämfört med vaken kirurgi.
List of papers

This dissertation is based on the following studies:

I) Deep Brain Stimulation in the caudal Zona incerta versus Best Medical Treatment in patients with Parkinson’s disease: a randomised blinded evaluation
Patric Blomstedt, Rasmus Stenmark Persson, Gun-Marie Hariz, Jan Linder, Anna Fredricks, Björn Häggström, Johanna Philipsson, Lars Forsgren, Marwan Hariz
Journal of Neurology, Neurosurgery and Psychiatry, 2018

II) Deep Brain Stimulation of caudal Zona incerta for Parkinson’s disease: One-year follow-up and Electric field simulations
Rasmus Stenmark Persson, Teresa Nordin, Gun-Marie Hariz, Karin Wårdell, Lars Forsgren, Marwan Hariz, Patric Blomstedt
Neuromodulation, 2021

III) Long-term follow-up of Unilateral Deep Brain Stimulation targeting the caudal Zona incerta in 13 patients with Parkinsonian tremor
Rasmus Stenmark Persson, Anders Fytagoridis, Maxim Ryzhkov, Marwan Hariz, Patric Blomstedt
Stereotactic and Functional Neurosurgery, 2023

IV) 10 years follow-up of Deep Brain Stimulation in the caudal Zona incerta/Posterior Subthalamic Area for Essential tremor
Yulia Blomstedt, Rasmus Stenmark Persson, Amar Awad, Gun-Marie Hariz, Johanna Philipson, Marwan Hariz, Anders Fytagoridis, Patric Blomstedt
Movement Disorders Clinical Practice, 2023

V) Awake and Asleep Deep Brain Stimulation targeting the caudal Zona incerta for Essential tremor
Rasmus Stenmark Persson, Yulia Blomstedt, Anders Fytagoridis, Marwan Hariz, Patric Blomstedt
Manuscript.

‘ Indicates shared first authorship.
Introduction

From the moment we are born to our last breath, we are in constant movement. Everyday actions such as walking, talking, eating, and even reading, all involve movement. The ability to perform, and the ease of how movements are performed, depend on an intact nervous system. Even the simple act of sitting down on a couch for some comfortable relaxation necessitates functional motor networks in the brain. Disruption in any part of these networks will negatively impact a person’s motor control, giving rise to an involuntary increase or decrease in movement. Diseases presenting in such a manner are called movement disorders. It is not difficult to imagine that these disorders can severely affect the autonomy and quality of life of the persons suffering from them.

This thesis is about neurosurgical treatment with Deep Brain Stimulation (DBS) of the two most common adult movement disorders: Parkinson’s disease (PD) and Essential tremor (ET). DBS aims at alleviating the symptoms of PD and ET by modulating dysfunctional signalling in motor networks of the brain through high frequency electrical stimulation. This is achieved by permanently implanting electrodes in structures deep in the brain and connecting them to an implantable pulse generator (IPG), or neuropacemaker, that sends out electrical current through the electrode. While there are many brain structures involved in the motor networks, this thesis will focus on DBS targeting an anatomical structure called the caudal Zona incerta (cZi).

To introduce DBS as a treatment for PD and ET in a clinically relatable setting, this background is written in the form of four different perspectives: The Neurologist, The Anatomist, The Neurosurgeon, and The Engineer. In the spirit of Euclid, we will start with the fundamental basics in order to establish what we do know, and then gradually narrow our perspective until we arrive at the questions at the centre of this thesis. This eclectic tale of the electric treatment of tremor will begin with the perspective of The Neurologist.
The Neurologist

*In examining disease, we gain wisdom about anatomy and physiology and biology. In examining the person with disease, we gain wisdom about life.* – Oliver W. Sacks

This perspective will concern the aspects of combining patient history, clinical observation, and examination to classify, diagnose and treat disorders of the nervous system.

**Tremor**

Tremor is defined as an involuntary, rhythmic, oscillatory movement of a body part\(^2\) and is present both in health and disease\(^3-5\). It is one of the most common neurological signs and is associated with hundreds of different causes\(^6,7\). The classification of tremors has varied throughout history and has been a topic for clinical and academic debate in recent years\(^8-13\). Regardless, tremor varies in activation condition, frequency, intensity, body distribution, and response to medication\(^10,14\).

There are two major divisions depending on activation condition: tremor with the body part at rest and tremor during action. Rest tremor is attenuated or absent during voluntary movement of the affected body part, whilst action tremor is absent during rest and only occurs with voluntary contraction of muscles. Action tremors can be subdivided into postural, kinetic, task-specific, and isometric tremor. Postural tremor occurs when maintaining a position, or posture, against gravity. Kinetic tremor occurs during any part of voluntary movement with one commonly mentioned subtype being intention tremor which is a crescendo increase, or occurrence, of tremor as the affected body part approaches a target.

The intention component can be especially disabling during actions such as drinking/eating and writing as a sudden increase in tremor when the glass/fork approaching the mouth can cause spill, and in the case of writing making it difficult to put the pen in the proper starting position to initiate writing e.g., a signature.

Tremor frequency is measured by the number of oscillations the body part does per second (Hertz, Hz). As such, it concerns the speed of the tremor and can be useful in classification but not as helpful in clinical diagnostics as most pathological tremors have a frequency between 4 and 8 Hz\(^13,15\).
The presence of other neurological signs is one of the most important aspects in differential diagnostics but at the same time somewhat controversial as there is some debate in what constitutes a part of normal aging, a tremor syndrome or as a sign of a specific disease such as PD\textsuperscript{2,9,16-19}. Regardless of the cause, tremor has been found to have a negative impact on several aspects of a person’s quality of life, affecting not only everyday functions such as drinking or writing but has also been associated with stigmatisation, social isolation and worse emotional well-being\textsuperscript{20-26}.

**Essential tremor**

The definition of ET has varied historically, both with regards to the characteristics of the tremor itself, and with regards to specific diagnostic criteria. In 2018, the Task Force on Tremor of the International Parkinson and Movement Disorder Society released an updated consensus statement on the classification of tremor. One main feature was the introduction of “ET plus”, meaning patients with the same tremor phenotype as ET but with additional soft neurological signs, such as mild cognitive impairment, gait disturbance and dystonic-like posturing.

Since then, several papers, including some from co-authors of the consensus statement, have raised issues with the new classification\textsuperscript{8,10,11,17,27,28}. Regarding ET plus specifically, some argue that the presence of certain soft signs is merely part of a more advanced stage of ET\textsuperscript{18,29}. Since the patients included in study IV and IV in this thesis were diagnosed with ET prior to this consensus statement, the term ET will relate to the previous definition\textsuperscript{13}.

**Epidemiology**

ET is the most common adult movement disorder and affects around 1% of the general population and up to 5-10% of elderly people\textsuperscript{30}. ET constitutes a heterogenous condition of clinically similar tremor phenotype with a reported rate of misdiagnosis up to 37-50%, sometimes being diagnosed as PD\textsuperscript{31-33}. Half of the cases of ET has a hereditary component\textsuperscript{14,34,35} and although more common among people over the age of 65, the age of onset varies across all ages and ET is known to debut even during childhood\textsuperscript{14,36-43}. 
While the cause of ET is still unknown, it is believed to arise from a disruption in functional networks involving the cerebellum, thalamus, motor cortex, and the brainstem\textsuperscript{44} (see \textit{The Anatomist}).

**Symptoms and diagnosis**

Since there is currently no disease-specific biological marker for ET, the diagnosis is based on clinical criteria. ET manifests itself with action tremor in both arms/hands with or without involvement of the head, voice, or lower limbs.

The tremor in ET is both of a postural and kinetic phenotype, although some argue that up to a third of patients develop rest tremor in the arm during advanced stages\textsuperscript{28,32,34,45-47}. It is mostly symmetric, sometimes with mild asymmetry, and up to half of patients have an intention component\textsuperscript{10,48-50}. The postural tremor develops quickly after the limb has established its posture, which distinguishes it from the postural re-emergent tremor seen in PD (see \textit{Parkinson's Disease}).

Although several soft signs such as mild ataxia, gait disturbance, and mild cognitive impairment have been associated with ET\textsuperscript{51,52}, the presence of clear neurological signs typical of other neurological disorders should warrant further investigation and are established exclusion criteria\textsuperscript{2,13}.

**Disease progression**

The older misconception that ET is a stable and benign disease is not reflected in modern studies. The natural course of the disease is understudied and speculated to differ between early and late onset ET, with the latter having a faster and more significant progression of tremor as well as a higher degree of associated symptoms\textsuperscript{36,53}. Longitudinal studies of ET have found an average annual increase in tremor severity between 3.1-12\%, with spreading of the tremor to other body parts and an increasing emergence of soft signs\textsuperscript{54,55}. This is also reflected in the patients’ own experience, with one study showing that more than half of patients with ET report a continuous worsening of tremor over a 5-year period\textsuperscript{56}.
This worsening over time can in many cases become debilitating, not only affecting the patient's ability to perform activities of daily living (ADL) such as working, eating, and writing, but also their social interactions, mood and psychiatric well-being as well\textsuperscript{20-22,57-62}.

**Treatment**
All therapies for ET are aimed at relieving symptoms as no curative treatment has been developed yet. First-line treatment with propranolol is known to relieve tremor to some degree in 50-70\% of patients. Discontinuation due to adverse events has been below 10\% in high-grade studies but known side effects include bradycardia and bronchospasm\textsuperscript{63}. Consequently, propranolol is contraindicated in people with asthma, which affects 10\% of the Swedish population.

The second-line drug commonly used, primidone, is often prescribed off-label. It has a good effect on tremor but interacts with the effects and metabolism of many other medications (at least 407 known interactions according to the Swedish drug registry Janusmed, accessed 2023-08-14). Primidone is also known to be discontinued in up to 42\% of patients due to a high degree of side effects such as malaise, unsteadiness, and dizziness, as well as depression, apathy, and sedation\textsuperscript{63}. One other drug, Topiramate, has been found to be efficacious in certain doses, but again commonly discontinued due to side effects. Other anti-epileptic drugs such as Gabapentin and Zonisamide as well as benzodiazepines have been found in smaller studies to have an anti-tremorous effect in some patients. These are often withdrawn due to insufficient relief, side effects, or habit-forming and habituating effects.

When pharmacological treatment has been found to be insufficient, unsuitable, or intolerable, neurosurgery in the form of lesional treatment or DBS is a clinically useful option for patients with debilitating tremor\textsuperscript{63-65}. 
Parkinson’s disease

In 1817, James Parkinson published his work “An Essay on the Shaking Palsy” describing his observations of six people with similar and progressively worsening symptoms. His aspirations with the work was to inspire nosologists to investigate this “most distressing malady.” In that, he succeeded, with historical neurologists such as Marshall Hall, William Gowers, and Jean-Marie Charcot expanding on the clinical features of this distinct entity. Notably, Charcot introduced the term PD as well as highlighting its key feature being bradykinesia. Since then, the classification of PD has evolved and although there have been great advances in the pathophysiology and possible cause of PD, it can still be considered a multi-etiologic syndrome as opposed to a defined disease. To clarify but still adhere to the established terminology, PD will henceforth be synonymous with idiopathic PD.

Epidemiology

PD is a neurodegenerative disorder affecting up to 20,000 people in Sweden and up to 10 million worldwide. Each year, around 20 out of 100,000 develop PD in Sweden and there has been a global increase in prevalence with the number of patients with PD projected to double in the upcoming decades.

Although several genetic and environmental factors have been linked to PD, the exact cause of the disease remains unclear. While it is now established that the degeneration affects several parts of the nervous system, the main pathological hallmark of PD has been the death of dopaminergic neurons in the substantia nigra pars compacta. It is important to recognize the widespread neurodegeneration and its effects on different networks as it probably explains the multifaceted expression of PD. However, to reflect the orientations of most treatment-related studies of PD, the following sections will gravitate around the consequences of this dopamine deficiency.

Diagnosis

Since the patterns of degeneration can only be ascertained post-mortem, the diagnosis of PD has been heavily dependent on clinical features. The disruption of the different networks results in both motor and non-motor symptoms.
The hallmark clinical feature of PD is a group of motor symptoms, collectively known as Parkinsonism consisting of bradykinesia, rest tremor, rigidity, and postural instability. Parkinsonism has been associated with over 50 different causes and misdiagnosis of PD is not uncommon. In a systematic review and meta-analysis of studies between 1988-2014 on the accuracy of clinical diagnosis of PD, the pooled diagnostic accuracy was around 80%, even among movement disorder experts.

Despite advances in imaging and biofluid biomarkers, the diagnosis of PD is still mainly based on neurological signs and associated symptoms. In 2015, the Movement Disorder Society published updated clinical diagnostic criteria in which postural instability was removed from criteria of Parkinsonism. Since postural instability mostly occurs in the later stages of PD, it was considered as an indicator of alternative diagnosis if being an early sign of disease. Whether these new clinical criteria, with or without the combination of imaging and biofluid biomarkers, will increase the accuracy of diagnosis of PD remains to be seen.

As now established, the motor symptoms have a central role in PD and as such, it is of interest to go into the details of Parkinsonism.

**Parkinsonian tremor**

The classic PD tremor is a 4-6Hz rest tremor of the fingers/hand/arm with a unilateral debut and dominance. It usually spreads to become bilateral and can involve the jaw, lips, and tongue. Some patients also report a sensation of internal tremor and can awaken due to the rest tremor. Characteristically, the tremor greatly subsides during voluntary movements and is often one of the presenting symptoms of PD, which may aid in differentiating it from the rest tremor seen in ET. Clinicopathologic studies have reported that 77-100% of PD patients experience rest tremor sometime during their life. Whether this discrepancy is due to the presence of tremor being a temporal aspect of PD or there being specific subtypes of PD without tremor has not been elucidated.

Besides rest tremor, studies have found that around 40-93% of PD patients have action tremor, either as a postural tremor or kinetic tremor. The reports are confounded by the fact that there seem to be two distinct types of postural tremor in PD.
A rest tremor that disappears with movement but reappears with a slight delay after the limb has reached a fixed posture is called **re-emergent tremor**. This re-emergent tremor occurs in around two thirds of patients with PD tremor and resembles rest tremor to a higher degree than postural tremor without rest tremor\(^\text{15}\). Another confounder of action tremor in PD is that there is evidence of correlation between ET and PD, with some arguing that there are forms of ET that evolve into or increase the risk of developing PD. Others argue that a co-occurrence of ET and PD in a single patient is mere coincidence since they are both relatively common disorders\(^\text{34,93-99}\).

Regardless, between 25-50% of patients with PD have tremor as a dominant symptom and tremor has been ranked as one of the most debilitating symptoms in patient surveys, even being cited as one of the main reasons for patients requesting surgical treatment\(^\text{24,100-102}\).

**Other Parkinsonian symptoms**

The obligate symptom of Parkinsonism is bradykinesia which means slowness of movement. Other terms used interchangeably with bradykinesia are *hypokinesia*, meaning diminutive movements, and *akinesia*, meaning no movement. In the context of clinical diagnosis of PD, bradykinesia is currently defined as both slowness and **progressive reduction in amplitude and speed** during repetitive movements\(^\text{77,103}\).

The third cardinal feature of PD is rigidity, meaning stiffness of muscles. This feature is due to a heightened muscle tone and is defined as an unvarying increased resistance within the range of passive movement of a limb\(^\text{13,77}\). A phenomenon called **cogwheeling** often co-occurs with rigidity and is when there are several short involuntary resistances/arrests during passive movement. Although common in PD, cogwheeling on its own is not considered as rigidity\(^\text{77}\). As with tremor, rigidity begins unilaterally and spreads slowly to involve both sides of the body, but remains slightly asymmetric throughout the disease\(^\text{104}\).

Other motor symptoms include dysarthria, dysphonia, restless legs, dysphagia, micrography, and festinating gait, freezing phenomena and many more.
Although the motor symptoms have been the focus of attention, PD is associated with a multitude of non-motor symptoms as well. Olfactory dysfunction, rapid eye movement sleep disorder, autonomic dysfunction leading to constipation, urinary and erectile dysfunction, and orthostatic hypotension are common symptoms in PD. Cognitive and mood-related symptoms such as dementia, depression, anxiety, and mania are also common in patients with PD\textsuperscript{105}.

**Disease progression**

As the disease progresses, the amount and severity of motor and non-motor symptoms increase. Although several ongoing trials are investigating ways to prevent or slow disease progression, there is no curative treatment for PD currently.

Progression of motor symptoms has two aspects: the shifting nature of response to medication and the development of increasingly debilitating motor features non-responsive to dopaminergic medication. As most patients diagnosed with PD receive treatment, this development will be explained in the next section.

The motor and non-motor symptoms of PD lead to a significant impact on the patient’s autonomy and quality of life\textsuperscript{106,107}. Tremor and perceived stigma have been found to be main components affecting the well-being of patients with PD\textsuperscript{24-26,108}. To prepare for, cope with and alleviate the symptoms of PD, it is necessary to involve multiple health care professions.

**Treatment**

All established therapies, medical and surgical alike, are aimed at relieving the symptoms of PD and can substantially improve the quality of life of the individual patient.

The staple treatment of PD aims at compensating for the loss of dopaminergic activity in the basal ganglia. This is primarily done with oral intake of drugs, mainly levodopa or dopamine agonists. Levodopa is chemically transformed in neurons into dopamine. Dopamine agonists work by activating dopamine receptors in the synapses between the neurons. As the body is normally metabolising dopamine and eliminating the drugs, there is a need to refill during the day.
In the early stages of PD, it is often sufficient to medicate with a long-acting medication once a day or with low doses of short-acting medication three times a day. As the disease progresses, the time interval between doses needs to be decreased to provide sufficient relief. Eventually, the intake can be as much as five to nine times a day. Other medications such as catechol-O-methyltransferase inhibitor, monoamine oxidase B inhibitors or apomorphine are available as adjunct therapies.

The efficacy of medication varies depending on the symptom. Bradykinesia and rigidity are in general quite responsive to dopaminergic medication while the effect on tremor is more unpredictable and tremor is known to be especially difficult to treat with medication. Additionally, axial symptoms such as gait- and balance disturbances are known to be poorly alleviated by dopaminergic medication.

The effectiveness of oral medication decreases as the disease progresses and eventually leads to debilitating changes between mobility and immobility, called motor fluctuations, and large, involuntary, choreatic movements called dyskinesia. The fluctuations can be predictable as loss of effect before the next dose intake or unpredictable and unrelated to the time of dose intake. Similarly, dyskinesia can occur shortly after medication intake, at the peak-of-dose or at the end-of-dose. This stage is often referred to PD with motor complications or moderate-advanced PD.

At this stage, when medication fails to provide sufficient symptom relief or is associated with motor complications, advanced therapies in the form of neurosurgery or medical pump-devices are established treatments. The current indications for invasive therapy are that the following symptoms have a moderate to severe impact on quality of life: motor fluctuations and/or dyskinesia and/or medically refractory tremor.

To understand how invasive surgery of the brain can alleviate symptoms in disorders relating to movement, it is necessary to have some knowledge about the structure and function of the nervous system. Although our understanding of the nervous system is due to works by several disciplines (molecular and cell biology, anatomy, physiology, pharmacology, neurosurgery, neurology etc.), this will be summarised under the auspices of The Anatomist.
The Anatomist

_Faced with an anatomical fact proven beyond doubt, any physiological result that stands in contradiction to it loses all its meaning...So, first anatomy and then physiology; but if first physiology, then not without anatomy._

- Bernhard von Gudden, psychiatrist, and pioneering neuroanatomist.

Organisationally, the nervous system can be likened to that of a computer or electric wiring diagram with different nodes and their connections, sometimes called a connectome. These nodes and their wiring have a structural and a functional aspect, and both will be integrated throughout this background. To clarify, the different nodes and connections mentioned in this background have been significantly simplified to their main parts rather than the immensely complex circuitry that is the human connectome.

On the microscale, the cells in the brain can be divided into two types: nerve cells, or neurons, and supporting glial cells. Almost all neurons communicate by generating electrical signals. Since the mechanism of DBS is believed to mainly be achieved by modulating these electrical signals, the focus will be on neurons.

**The main nodes and their wiring**

The main nodes involved in the sensorimotor network are the cerebral cortex, the basal ganglia, the thalamus, and the cerebellum. **Figure 1** highlights the specific structures important in DBS for PD and ET.

The cerebral cortex lines the surface of the brain and the discovery that some cortical regions are directly involved in motor control date back to late 19th century. Experimental studies on animals revealed that electrical stimulation of different parts of the cortex elicited movement of different body parts. This existence of a motor cortex was later confirmed in non-human primates as well as humans. Other distinct motor areas in the frontal lobe, as well as other cortices such as the sensory and the associate cortex are involved in the generation of appropriate movement.
The **basal ganglia** (BG) consist of a functionally diverse set of grey matter nuclei that are deeply seated within the brain. The parts of the BG involved in the motor network are the **striatum** (nucleus caudatus and putamen), the **pallidum** (globus pallidus interna and externa, GPi and GPe), the **subthalamic nucleus** (STN), and **substantia nigra** (pars reticulata and compacta, SNr and SNC). The BG have widespread connections with the cerebral cortex and the thalamus, as well as the brainstem and the cerebellum. The striatum and the STN act as main input nodes into the BG while the GPi and the SNr act as the main output nodes. The different structures of the BG are interconnected through fibre tracts.

**Figure 1.** Coronal view of the brain with key anatomical structures involved in DBS for PD and ET. For clarity the structures have been placed in the same plane, but it should be noted that some are in different locations in the antero-posterior direction than shown here.
The thalamus is a bilateral group of nuclei located in the centre of the brain. These nuclei receive and send projections to all major parts of the central nervous system. The delineations and functions of specific thalamic nuclei have been and are still subject to debate. Further, nomenclature is heterogeneous, in part due to differences between anatomists and neurosurgeons but also between human, primate and rodent anatomy. The major nuclei involved in motor control are the Ventral Lateral part of the thalamus (VL), often subdivided into the Ventral Lateral anterior (VLa), Ventral Lateral posterior (VLp) and Ventral Posterior Lateral anterior division (VPLa). Neurosurgical studies, often cited as using the neuroanatomist Rolf Hassler’s nomenclature, commonly uses the Vim, ventral intermediate nucleus, as anatomical target which according to harmonisation efforts would correspond to VLp. However, Vim defined by electrophysiology might also include parts of VPLa and Hassler specified that the ventral oral posterior (Vop) nucleus received cerebello-thalamic projections, not the Vim. Regardless, the main segregation used in this thesis is based on the origin of the projections to the individual nucleus; mainly the cerebellar-receiving VLp/Vim/Vop and the pallidal receiving VLa/Voa. The terms will be used interchangeably in this thesis, with Vim mainly referring to the surgical treatment target whilst VL will mainly be used in network/pathophysiological sections.

The cerebellum is located below the brain and behind the brainstem. It is composed of cerebellar cortex and nuclei and contains more neurons than the cerebral cortex itself, despite being a fraction of its volume. The cerebellum has reciprocal projections to the cerebral cortex and receives input from the inferior olive, spinal cord, and the vestibular system. Cells of the dentate nuclei send mostly contralateral, but some ipsilateral, projections to the midbrain and pass near and partly through the red nucleus (RN) to terminate in the VL thalamus. The main output projection relevant to this thesis is the dentato-rubro-thalamic tract (DRTT) as part of the cerebellothalamic tract (CTT), a key component of the cerebral cortical-cerebello-thalamo-cortical circuit.
It was for a long time thought that the subcircuits of the BG and the cerebellum had independent but complementary functions in motor control and any interactions occurred on the cortical level. However, advances in recent decades have made clear that these nodes and subcircuits do not operate individually but instead directly interact with each other to improve current and future motor actions\textsuperscript{120}. Currently, the BG is thought to assist the cortical motor areas to decide if, when and how vigorously a specific motor program should be executed while the cerebellum acts by finetuning the movement through predictions based on real-time feedback\textsuperscript{117,121}. It is also believed that the BG are mostly involved in reward-based learning while cerebellum is mostly involved in error-based learning, although this distinction is possibly crude\textsuperscript{122}. 
Posterior Subthalamic Area: Zona incerta and its neighbours

Directly below the posterior thalamus is a structurally interesting but complex region (see Figure 2 on the next page). This area contains nuclei, such as the STN and RN, as well as crossing fibre tracts such as the medial lemniscus, CTT and the pallidothalamic tract (PTT) involved in the cerebello-thalamo-cortical and cortico-basal ganglia-thalamo-cortical circuits. The nomenclature regarding the region itself and its anatomical components has varied throughout history, and a common consensus is still lacking.

The small region between the STN and RN is called the posterior subthalamic area (PSA), which is a practical denomination to distinguish it from the STN and VL thalamus themselves as targets for stereotactic functional neurosurgery. Its principal components are the Zona incerta (Zi) and fibre tracts called prelemniscal radiations (Raprl), neighbouring the fields of Forel (H0/H1/H2) although these have sometimes been included as part of PSA.

The first to describe Zi was the anatomist August Forel, the namesake of fields of Forel and student of von Gudden quoted in the beginning of this chapter. Forel wrote in 1877 that Zi was a region of which nothing certain can be said. 130 years of revolutionary development within neuroscience later, it arguably remains one of the least studied regions of the brain.

Although there has been an increased interest in exploring the connections and function of Zi in recent years, most knowledge about Zi anatomy and physiology come from studies on rodents and non-human primates. Zi can be considered an extension of the reticular nucleus of the thalamus but lies as a separate structure directly below the thalamus. Zi runs above (dorsal) to the STN and drapes along the medial border of the STN terminating in the so-called "Q-area" where it is called caudal Zi (cZi). The part dorsal/dorsomedial to the STN is in clinical DBS-studies often referred to as rostral Zi.
Introduction/The Anatomist/Posterior Subthalamic Area: Zona incerta and its neighbours

The distinct location of the cZi, lying directly posteromedial to the posterior tail of the STN, is the main reason why the denomination of “cZi-DBS” is used in this thesis (see The Neurosurgeon). The different parts of Zi vary in cyto- and chemoarchitecture, and results from animal studies have suggested that the cZi may have a distinctly different function than the remainder of Zi\textsuperscript{131,132}. Of note is that there is no distinct border between the different sections.

Zi has widespread connections to deep cerebellar nuclei, thalamus, BG (SNC/r, GPI/e), cerebral cortex, brainstem, and the spinal cord, as well as the contralateral Zi. Some of these are reciprocal and Zi also contain interneurons\textsuperscript{133}. The centrocaudal part of the Zi is traversed by cerebellothalamic fibres of which some form collaterals to terminate in the Zi, while the majority terminate in the VL thalamus. The medial Zi sends dopaminergic projections to several structures such as the hypothalamus, amygdala, the pedunculopontine nucleus and the cuneiform nucleus.

**Figure 2.** A coronal view of the posterior subthalamic area and the surrounding relevant anatomy. This is a schematic representation as the different structures are not located along the same plane. CTT = Cerebellothalamic tract, PTT = Pallidothalamic tract, VLP/Vim = cerebellar-receiving nucleus of the thalamus, VLA/Voa = pallidal-receiving nucleus, fl = fasciculus lenticularis, al = ansa lenticularis
Functionally, Zi has been speculated to have a role in arousal, attention, visceral, and locomotor function\textsuperscript{130,132-135}. Although there are some conflicting results regarding the presumed role of Zi in motor control, several experimental animal studies have found that selective lesions or pharmacological manipulation of the Zi influence motor behaviour and can induce or counteract symptoms similar to bradykinesia and rigidity\textsuperscript{133}.

The other main component of PSA is the Raprl, which according to Morel et al. mostly corresponds to the CTT originating in deep cerebellar nuclei, namely the dentate, interposed, and fastigial nuclei\textsuperscript{123,136}.

CTT travels through the superior cerebellar peduncle, then most of the fibres cross over its decussation and pass through and anterior to the RN and terminates mainly in the posterior part of VL thalamus. In the same manner as the corticospinal projections converge in a funnel-like manner from the cerebral cortex down through the internal capsule, so does the CTT within the PSA.

The PTT is more complex in its course and is divided into smaller bundles; the fasciculus lenticularis (fl) and the ansa lenticularis (al), which merge to form the fasciculus thalamicus (ft). Al leaves the GPi anteroinferiorly and travels in front of and medial around the posterior limb of the internal capsule. From here, the al continues down then up towards the thalamus where it is joined by the fl arriving over the dorsal part of the STN.

The fl leaves the medial GPi, crosses the posterior limb of the internal capsule and emerges after into what is known as H2 of Forel. Fl travels above the STN but below the Zi in a posteroinferior direction, joining the al to form ft (H1+H2 of Forel). The term ft encompasses all pallidofugal fibres regardless of origin, denominated as PTT above. The PTT enter the VL thalamus just anterior to the entry of CTT (VLa).
The Tremor Networks

The thalamus has long been seen as a key region in the functional networks involved in generating tremor as it transmits information both from the BG and the cerebellum back to the motor cortex. This view is partly based on the fact that strategic lesions within and below the VL thalamus alleviate tremor and that tremor-specific activity has been recorded in that area\textsuperscript{137,138}. As previously mentioned, PD tremor is variable both in expression and prevalence in the PD-population, and in its response to dopaminergic treatment. In addition, the severity of tremor in a PD patient neither seem to correlate to other PD symptoms\textsuperscript{89} nor has the same progression over time\textsuperscript{139,140}. This has led to the suggestion that tremor has a distinctly different pathophysiology than the other PD symptoms.

In 2011, Helmich et al. introduced the \textit{dimmer-light switch model} to explain the generation, modulation, and maintenance of PD tremor by the involvement of both the basal ganglia-network and cerebello-thalamo-cortical network both with separate functions as well as the interplay between them\textsuperscript{141-143}. In essence, the BG act as a light switch, turning on/off the tremor whilst the cerebello-thalamic subcircuit maintains the tremor and the motor cortex modulates the amplitude of the tremor as a dimmer (see Figure 3).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Figure3.png}
\caption{The dimmer-light switch model of Parkinsonian tremor. The coloured regions indicate where tremor-related activity has been found. Blue = Basal ganglia. Red = Cerebello-thalamocortical circuit.}
\end{figure}

\textit{CBLM} = cerebellum, \textit{RRA} = retrorubral area, \textit{LC} = Locus coeruleus.

\textit{Taken unedited from Helmich 2018\textsuperscript{143} with permission from John Wiley and Sons.}
There is a common viewpoint that the cerebello-thalamo-cortical circuit is also involved in ET\textsuperscript{144,145}. Results from animal models, clinical observations, pathological, neurophysiological, and imaging studies all support the notion of dysfunctional oscillations in this network as the mechanism of ET (see Figure 4)\textsuperscript{121,144-146}. Although a primary origin of the oscillations has not been conclusively determined, disrupting these oscillations seem fundamental to the treatment of ET. A recent review connected these two models of PD tremor and ET to the common link that is the cerebello-thalamic subcircuit\textsuperscript{147}.

\textbf{Figure 4.} Structures with findings related to ET. Red regions are mainly associated with the cerebello-thalamo-cortical circuit while blue regions with the BG circuit. Arrows depict structural connections between the regions.

\textit{DN = dentate nucleus, DCN, deep cerebellar nuclei, SMA = supplementary motor area. Taken unedited from van den Berg and Helmich 2021\textsuperscript{146}.}
**The Parkinsonism Network**

In 1989 and 1990, two landmark papers introduced a functional anatomical model of the BG that was capable of reconciling hyperkinetic (choreiform) and hypokinetic (bradykinesia) symptoms to a dysfunction in the same circuitry due to altered dopaminergic signalling in the striatum\(^{148,149}\). This standard model of pathophysiology of Parkinsonism was widely accepted and has been the foundational view of the circuitry involved in PD over the last three decades\(^{150}\). According to this model, the BG are nodes in several mostly segregated, parallel cortical-subcortical circuits which have roughly been divided into the motor, oculomotor, prefrontal, and limbic circuit.

Recent developments in anatomical tracer-studies, as well as the introduction of dynamic modelling, have mostly replaced the view of segregated, linear circuits with a more nuanced and interconnected network\(^{151-153}\). As it stands, a more complete new model has yet to be presented and the standard model still has some use to introduce the pathophysiological basis of some of the motor symptoms of PD.

The motor circuit begins in the motor areas of the cerebral cortex (see **Figure 5**). There are then three functional pathways through which signals travel to and through the BG: the direct, indirect and hyperdirect pathway. The main output nuclei of the BG are the GPi and SNr. These nuclei are tonically active and send inhibitory projections to the VL thalamus and brainstem. Thus, input from motor areas is thought to be processed in the BG with input from other cortical areas, with the output modulating thalamo-cortical circuits and brainstem circuits through inhibition. In other words, the BG modulates motor behaviour by putting the brakes on activity in the thalamus and brainstem.

Both the direct and indirect pathway begin with cortical projections to neurons in the sensorimotor part of the striatum. These neurons can then either send monosynaptic projections to the GPi and SNr (direct pathway) or to the GPe (indirect pathway). The GPe sends projections back to the striatum as well as to both the STN and the GPi/SNr. Finally, the STN sends projections back to the GPe as well as to the GPi/SNr. The projections within the BG are inhibitory (gamma-aminobutyric acid as main transmitter, GABA-ergic) except for the STN which sends excitatory projections.
The STN also receives direct input from the cortex through the hyperdirect pathway. The output of the striatum is modulated by dopaminergic projections from the SNc.

According to this model, the decreased dopaminergic influence on the striatum in PD leads to an increased inhibition of the thalamocortical subcircuit, resulting in slower and smaller movements and initiation difficulties\textsuperscript{150}.

As such, the different nuclei within this circuit, and their projections, are potential targets for therapies such as DBS\textsuperscript{116}.

Now that we have established that PD and ET are debilitating disorders with shared clinical, anatomical, and pathophysiological features, it is time to introduce the perspective of \textit{The Neurosurgeon}.
The Neurosurgeon

Functional neurosurgery aims at restoring function, mostly through symptom alleviation. By using a technique called stereotaxy, or stereotactic neurosurgery, it is possible to affect deeply seated brain structures with millimetre precision.

Stereotactic functional neurosurgery, either by creating precise lesions or implanting DBS-systems, are established surgical treatments for PD and ET when pharmacological treatment is insufficient.

To understand how DBS of different brain targets became a definite part of the treatment of PD and ET, a historical review can be enlightening. Those less historically inclined are invited to skip to the DBS-section on page 26.

Stereotactic Functional Neurosurgery

Stereotactic surgery entails creating a three-dimensional cartesian coordinate system of the patient’s brain by mounting a frame on the patient’s head in combination with radiological imaging.

This technique was developed in the hopes of reducing mortality rates and side effects of open lesional neurosurgery performed in the first decades of the 1900s. In 1947, on the backbone of stereotactic techniques used for animal research, Austrian-American neurologist Ernst Spiegel and neurosurgeon Henry Wycis developed a stereotactic frame for human neurosurgery\textsuperscript{154}. Although initially used for psychiatric surgery, the frame-based approach also became widely utilised for surgery for movement disorders\textsuperscript{155}.

By using a frame and combining it with radiological imaging to identify anatomical landmarks, it became possible to create precise lesions in deep parts of the brain with a simple burr hole and with minimised impact on more superficially located structures. Different teams used and developed different frames and tools to create a lesion but the principle of using a coordinate-based system and a probe was the same\textsuperscript{156}.

Previously, American neurosurgeon Russel Meyers had shown that open selective resection of the pallidum and its outflow fibre tract ansa lenticularis reduced tremor. In 1951, another American neurosurgeon Irving Cooper made the serendipitous discovery that degeneration of the
GPi caused by ligation of the anterior choroid artery decreased Parkinsonism. Together, the GPi and its outflow fibre tracts became logical targets for stereotactic lesional surgery\textsuperscript{157,158}.

During the following decades, thousands of patients were treated with lesional surgery for movement disorders with good effect on tremor and rigidity. New targets for lesional surgery were discovered during this time. The VL thalamus was introduced as a target for tremor based on anatomopathological studies by German anatomist Rolf Hassler and neurosurgeon Traugott Riechert in addition to the discovery by Cooper that one of his patients with a successful pallidotomy actually had a lesion in the VL thalamus\textsuperscript{157}.

During these lesional procedures, it was common to test the location of the probe before performing the final lesion, using electrical stimulation\textsuperscript{159}. This resulted in an exploration of the thalamus and nearby structures as potential targets for lesional surgery for movement disorders. During the Third Symposium on Parkinson’s Disease in 1968, the Scottish neurosurgeon John Gillingham presented a compilation of locations where lesions had been proven to alleviate “tremor, rigidity and some of the other symptoms of Parkinsonism” (see Figure 6)\textsuperscript{160}. It clearly shows a pathway extending from the GPi to the VL thalamus and down into the PSA in between the RN and the STN where Zi, CTT and PTT are located.

During the same symposium, F. Mundinger summarised the results of 500 subthalamotomies on PD symptoms while B. Nashold and G. Slaughter reported the consistent cessation of PD tremor by electrical stimulation in this subthalamic region.
In addition, Bertrand et al. specifically mention a pronounced stun effect on tremor when introducing the electrode just a few millimetres below the VL thalamus, into the PSA, as demonstrated in Figure 7.

![Figure 7. Visualisation of where an electrode can end up in the PSA when targeting the VL thalamus by simply introducing the electrode a few millimetres deeper. As is shown, the distal part of an DBS electrode would end up in the caudal part of Zi.](image)

In fact, what was called thalamotomy sometimes ended up being lesions in the subthalamic area. Some neurosurgeons even preferred the subthalamic area over the thalamus itself as a target for tremor.

During this “lesional era”, thousands of patients were treated with thalamotomies, and subthalamotomies, for PD and tremor. Lesional surgery was a primary therapy for these disorders between the advent of stereotactic surgery in the late 1940s up until the introduction of levodopa in the 1960s. However, lesional surgery was limited to mainly be a unilateral procedure due to the increased risk of developing lasting side effects such as dysarthria, dysphagia, gait disturbances, and cognitive decline when performing bilateral lesions. The number of stereotactic procedures performed for movement disorders drastically reduced since levodopa became widely available. The advantages of a safe and effective oral medication over an invasive method almost made lesional procedures obsolete in the clinical setting.

In the following decades, surgical treatment of movement disorders was of limited importance up until the late 1980s-early 1990s. The renaissance of stereotactic functional neurosurgery was mainly due to three pivotal discoveries.
The first addressed the limitation of unilateral treatment for disorders with bilateral symptoms as is the case for both PD and ET. Alim Benabd, Pierre Pollak and their team in Grenoble, France, combined lesion in the VL thalamus (Vim) with implantation of a thin electrode in the contralateral Vim. By connecting the electrode to an implantable pacemaker, they could continue electrical stimulation outside of the surgical theatre\textsuperscript{164}. They were able to reduce the patient’s tremor on both sides of the body without the debilitating side effects known from bilateral lesions. This is seen as the advent of modern DBS, although chronic depth electrical stimulation as a therapy had been performed by several others previously\textsuperscript{164}.

The second discovery came from Umeå by Lauri Laitinen et al. who reintroduced Lars Leksell’s technique for posteroventral pallidotomy as a treatment for PD. Patients with PD had been treated with levodopa for several years and the limitations and side effects of long-term high dose treatment were evident. Debilitating levodopa-associated complications such as motor fluctuations and dyskinesia had created a new phenotype of PD that was difficult to treat with medication. Laitinen et al. demonstrated that posteroventral pallidotomy not only improved Parkinsonism but dyskinesia and motor fluctuations as well\textsuperscript{165}.

Thirdly, on the basis of the standard pathophysiological model of PD, Hagai Bergman, Thomas Wichmann and Mahlon DeLong hypothesized and reported in 1990 that lesional surgery of the STN alleviated Parkinsonism in animal models of PD\textsuperscript{166}. Within a few years, this was replicated by others and translated into clinical studies. In 1993, the team in Grenoble reported on the first human STN-DBS for PD and a few years later showed that bilateral STN-DBS was able to alleviate Parkinsonism without inducing hemiballismus, a feared side effect of lesions in the STN\textsuperscript{167,168}.

As such, the Vim, the GPi and the STN became the prime targets used for stereotactic functional neurosurgery for movement disorders. Since then, DBS has become the preferred approach whilst lesional procedures have only been performed in selected cases\textsuperscript{169}. One advantage with DBS in comparison to lesional procedures has been that the surgery can be performed bilaterally in the same session and that any side effects are mostly reversible. Most side effects caused by the stimulation can often be avoided by modifying the stimulation parameters\textsuperscript{163,164,170}.
Deep Brain Stimulation

It has been estimated that over 230 000 patients have been implanted with DBS-systems for various conditions with PD being the most established indication\textsuperscript{171}.

**Hardware**

DBS consists of three major components: implantable pulse generator (IPG), connection cables and electrodes. The IPG delivers electrical stimulation to the brain through contacts on the electrodes. The main delivery method has been constant voltage (V), meaning that the delivered energy fluctuates depending on the properties of the hardware and tissue impedance around the electrode. Newer manufacturers provide constant current programming (mA), resulting in a consistent electric field output.

The most used electrode is 1.27mm in diameter and has four concentric contacts. The contacts are 1.5mm in height and have a spacing between the contacts of 0.5mm or 1.5mm depending on the model. One or more contacts can be activated, and they can have different polarity (anodic/cathodic, see *The Engineer*). Commonly, one contact is activated as a cathode, called monopolar stimulation, while if two contacts of different polarity are used, it is called bipolar stimulation.

The IPG can be programmed using three main stimulation parameters: amplitude (V or mA), pulse width (microseconds, µs) and frequency (Hz). Typically, a pulse width between 60-120µs and a frequency between 130-180Hz are used for PD and ET.

After implantation, it is common to screen the effects of each individual contact in what is called a monopolar review. This entails activating one contact at a time and in a stepwise manner increase the amplitude of the stimulation and record the effects of each step.

When consistent intolerable side effects are produced, the amplitude is recorded, and the same process is repeated for the next contact. This results in a therapeutic window of each contact in which the patient gets symptomatic relief but without consistent side effects. The stimulation setting producing the most beneficial effects without consistent side effects are used for chronic stimulation.
Commonly, the parameters are adjusted several times over the course of weeks-months as some effects and side effects take time to develop. Additionally, patients may need to adjust their medication.

**Surgical technique**

As previously mentioned, the implantation of DBS is a form of stereotactic neurosurgery. The different types of surgical techniques used to implant DBS are enough to fill entire books, which goes outside the scope of this thesis. I have chosen to go into detail on a few pertinent aspects of the frame-based procedure to give a background on why these might be important for the outcome and safety of the procedure, or for the comfort of the patient. The entire procedure can be summarised in the following steps:

I) Mounting of the frame with four screws to the skull  
II) Pre/perioperative stereotactic imaging  
III) Planning of the surgical target (and trajectory) and coordinate calculation  
IV) Incision, burr hole and creation of electrode track  
V) (Intraoperative neurophysiological testing)  
VI) Electrode placement  
VII) Location verification  
VIII) Implantation of IPG and connection cables

Stereotactic imaging is used to localise anatomical landmarks, mainly the anterior and posterior commissure (AC-PC). These landmarks are used to create an origin of the coordinate system, typically the midcommissural point (MCP). X denotes the distance lateral to the MCP, Y behind or in front of the MCP and Z below or above the MCP/AC-PC-line. The images can also be used to visualise and identify the brain target.

Results from the lesional era led to statistical coordinates of the different targets based on post-mortem atlases and ventricular landmarks. Predefined coordinates is still used today but may result in poorly placed electrodes, due to significant interindividual anatomical differences. Instead, by performing preoperative magnetic resonance imaging (MRI), it is possible to visualise some of the anatomical targets and thereby directly target them in an individual patient.
The STN and the GPi can be visualised and directly targeted using standard MRI protocols, while the Vim cannot\textsuperscript{173,174}. Instead, for Vim-targeting, statistical atlas-coordinates or algorithms based on the length and width of AC-PC are used. While the cZi itself is not visible on MRI, it’s close relation to the STN and the RN makes it possible to reliably target using mental helplines (See Figure 8)\textsuperscript{175-177}.

Since the electrode has four contacts available for stimulation of which only one will be located near the visualised target below, a comprehensive explanation of the targeting method is necessary.

The targeting approach our group use is based on the following steps:

1) On axial images, determining the depth based on the maximal diameter of the RN, often 3-5mm below the AC-PC-level = Z-coordinate.

2) Drawing a mental help line, through the centre of the red nucleus and typically within 1mm of the posterior tail of the STN (pSTN) and placing the target at this line or 0.5mm posterior, generally located 7-8mm behind the MCP = Y-coordinate.

3) Determining the lateral border of the RN and placing the target 1/3-1/2 of the distance from the pSTN, typically between 10-13.5mm lateral to the AC-PC-line = X-coordinate.

4) Place the entry point within 10mm in front of or behind the ipsilateral coronal suture at the top of a gyrus (close to the calvarium) as medial as possible without the trajectory passing

\textbf{Figure 8.} The target (orange marker) based on axial slices with helplines. As the relation between RN and pSTN are different between atlases, as well as patients, the target marker is placed in a position which would be deemed as adequate lead placement. \textit{Left: Location of cZi in relation to pSTN. Middle: Axial T2 MRI. Right: A cropped axial slice from Stereotactic Atlas of the Human Thalamus and Basal Ganglia by Anne Morel\textsuperscript{136}, 2007 © Informa Healthcare USA.}
through sulci or ventricles. The entry is typically located 30-45mm lateral to the midline.

5) Following the trajectory and ensuring that the centre of the most distal contact ends up in the target and that the rest of the contacts end up medial to the STN.

Regardless of using atlas-based coordinates or visual anatomical targeting, there are various methods of verifying the brain target intraoperatively. Traditionally, the surgery has been performed with the patients awake which provides two main opportunities to evaluate and correct the target before fixation of the permanent electrode:

I) **Macrostimulation:** When proximity to the target has been established, it is possible to evaluate potential effects and side effects of stimulation using a radiofrequency electrode or the DBS electrode used for implantation.

II) **Microelectrode recording (MER):** By inserting several thin electrodes, it is also possible to record and analyse neural activity which gives an indication of where in the brain the electrodes might be seated. MER can be used on its own or in combination with macro- or microstimulation.

After the recording and testing-session is completed and the physiological target has been ascertained, the DBS electrode is placed at this location.

Another way of verifying electrode location is to use post implantation imaging. By using post implantation MRI or merging post implantation CT to the preoperative MRI, it is possible to visualise the electrode artifact in relation to the visualised anatomical targets.

While most agree that the most important step of DBS surgery is to ensure correct placement of the electrode, there is a disagreement regarding whether biosignatures or imaging best reflect the actual target. In 2016, reports from North American health care programs found that between 15.2-34% of over 28,000 implanted intracranial electrodes were revised or removed. Half of the cases seemed to be due to misplaced electrodes. Notably, MER was used in 87.3-90.4% of cases.
Neurophysiological testing is an invasive method necessitating considerable resources (neurophysiological equipment, dedicated neurologists, and neurophysiologists etc.). It has also been associated with an increased risk of haemorrhages, since it involves creating several tracts in the brain and introducing sharp cannulas into the target area.178 Further, the increased duration of open dura can increase the risk of introduction of air into the skull, resulting in brain shift and possible misplacement of the electrode.179 In addition, the similarity of neurophysiological signal patterns between adjacent structures, such as the RN and the STN, has been found to cause misplacement.180

If one can achieve the same effect using macrostimulation or MER but by only using visual anatomical targeting, several of the above-mentioned pitfalls or targeting issues can be circumvented.

**Awake and Asleep surgery**

While DBS has traditionally been performed awake to test and verify the physiological target, some disorders (severe dystonia) or patient categories (children) were performed with the patient asleep out of necessity. With the advances of visual anatomical targeting, and that MER can now be performed despite sedation-induced biosignatures, there has been an increased interest in performing asleep surgery.181-183 Several centres have performed asleep STN- and GPi-DBS for PD for years, seemingly without a decrease in effect of the treatment. However, as the primary target used for tremor (Vim) is not readily visible on MRI, most DBS surgery for tremor is still performed awake, even in centres doing STN- and GPi-DBS under general anaesthesia.

There are several potential advantages of image-guided asleep DBS. Firstly, with the patient asleep, the patient can lie in the same position during surgery as during the MRI-scans (horizontally) which gives a better correlation between planned images and brain position during surgery. Further, it may also lead to less leakage of cerebrospinal fluid (CSF) due to the brains position in the skull, as well as significantly shorter time with an open dura as there is no time-consuming test stimulation or MER. This is relevant as a brain shift due to excess CSF-leakage could affect the accuracy of the electrode placement. In addition, there are several other potential benefits of asleep DBS such as increased patient comfort and reduced surgical time.184
The literature is skewed regarding awake versus asleep DBS with up to 10 times the number of awake procedures published. There is further the issue of the definition of “asleep” surgery, with some groups calling sedation without complete general anaesthesia ‘asleep’ DBS to be able to use MER\textsuperscript{184}. Regardless, there is a great paucity on results of asleep DBS for ET.

**Targets**

During the first decade of the 2000s, several large randomised and/or blinded trials showed that bilateral STN- and GPI-DBS alleviate Parkinsonism, motor fluctuations, dyskinesia, and improve quality of life in patients with PD. In addition, experiences from the previous decade showed that Vim-DBS significantly alleviates tremor, perhaps to a higher degree than STN- and GPI-DBS, but not the other parkinsonian symptoms\textsuperscript{64,185-188}.

Around the same time, several studies reported psychiatric side effects following STN-DBS such as hypomania, apathy, depression, or suicide\textsuperscript{189-193}. In addition, the effects of STN-DBS were found to mainly affect symptoms responsive to levodopa and that levodopa-responsiveness is an individual predictor of successful treatment\textsuperscript{194,195}. Regarding Vim-DBS for tremor, side effects such as dysarthria, gait/balance disturbance and ataxia were well known, especially after bilateral procedures\textsuperscript{196}. Further, both regarding effects and side effects, the results may deteriorate over time for both STN- and Vim-DBS\textsuperscript{197-200}.

The PSA as a good surgical target for alleviating tremor and rigidity was forgotten during this first decade of modern DBS, mostly due to the success of Vim, STN, and GPI as targets for DBS. However, in the early 2000s several groups revived various structures in the PSA as a target for DBS\textsuperscript{201-205}. Open label studies reported good results of DBS in various parts of the PSA for different forms of tremor, including PD tremor\textsuperscript{206-214}. In addition, PSA-DBS was found to improve bradykinesia and rigidity as well. Complications and side effects of PSA-DBS have been found to be mild, and mostly transient\textsuperscript{175,215}. Although side effects such as dysarthria, gait disturbance and ataxia were also found following PSA-DBS for ET, none of the studies on PD have reported psychiatric side effects that resemble what had been described following STN-DBS.
In 2006, one study compared STN- and cZi-DBS in a non-randomised non-blinded manner, and suggested the latter to be more effective, not only for tremor, but also for rigidity and bradykiniesia.\(^\text{210}\) In addition, a systematic review of reported locations of STN-DBS found that a majority of contacts used for stimulation was on the border or outside of the STN.\(^\text{216}\) In a similar manner, studies targeting the Vim have found that the active or most effective contacts for stimulation are sometimes located in the PSA.\(^\text{217-220}\) Recently, two large reviews of published papers on PSA-DBS for various movement disorders have concurred in that this procedure seems to be quite efficient for tremor.\(^\text{213,214}\) However, one review pointed out the need for blinded evaluations,\(^\text{213}\) and the other review pointed to the need for quality of life assessments of patients.\(^\text{214}\)

Today, STN is the most common target for PD, partly due to a significant reduction of levodopa dosages which GPi-DBS does not affect, while Vim is the most used target for ET. For some patients with PD, the Vim or the GPi are preferred according to the symptomatic profile or other patient-specific considerations.\(^\text{221-223}\)

**Estimation of anatomical location**

Several aspects are important to ensure a satisfactory effect of DBS, including patient and target selection, optimised stimulation parameters and medication, physiotherapy, and psychological support to adapt to the changes following DBS. Another important aspect is the correct placement of the electrode.

During the lesional era, the correlation between symptom alleviation and anatomical location was determined in part by post-mortem studies and in part through the exploration of a target’s surrounding area during surgery. As Gillingham showed in 1968 (Fig. 5) the effects were not contained to a single spot but several different but interconnected anatomical structures. Further, in 1978, Kelly et. al. analysed the location of 100 lesions in the thalamus in patients with PD tremor or intention tremor.\(^\text{224}\) They superimposed the locations of the lesions resulting in complete abolition of tremor on locations where there was a continuation, recurrence, or incomplete alleviation of tremor. They found that these locations were
virtually completely overlapping. Paradoxically, it seemed that despite the best efforts of several decades of stereotactic functional neurosurgery, an optimal location, a sweet spot, where a lesion most reliably alleviates tremor and Parkinsonism had not been found.

As is known, history repeats itself, and the reintroduction/rediscovery of different targets from the lesional era into the DBS-era follow the same pattern. Concurrent with discussions on patient selection, levodopa-responsive symptoms and so forth, the exploration for a sweet spot of where DBS leads to a good effect has been ongoing. Paradoxically, it seems that despite the best efforts of several decades of stereotactic functional neurosurgery, a sweet spot where DBS most reliably alleviates tremor or Parkinsonism is still being debated\textsuperscript{225,226}.

Finally, stimulation parameters vary between patients, diseases, studies and over time\textsuperscript{64,227-229}. As the effect of DBS relates to the specific settings, especially with regards to amplitude and pulse width\textsuperscript{230,231}, it would be appropriate to account for this when correlating the clinical effect to the anatomy.

This leads to electric field simulations, which encompass the method of using mathematical models to simulate the spread of electric current around the electrode. In the last decade, there has been an increased interest in using electric field simulations, both to find optimal/suboptimal location for stimulation in known DBS-targets (sweet/sour spots) as well as to assist in predictive programming as the electrode design has reached a new complexity. This concept will be introduced from the perspective of The Engineer.
The Engineer

This perspective will introduce how it is possible to use computational models to better understand the clinical effects of DBS in relation to the anatomy. The goal of this chapter is to provide enough information to understand the benefits and limitations of the models shown in the results chapters of this thesis. To be able to draw conclusions about the effects of DBS using these models, there are two main parts: patient-specific simulations and group analysis.

Patient-specific simulations

There are two basic aspects of computational modelling of DBS:

I) A model of the electric field generated around the electrode e.g., Finite Element Method (FEM)

II) A model of how neurons react to the electric field e.g., Volume of Neural/Tissue Activation (VNA/VTA)

To introduce these models, it is necessary to review the biophysical principles of DBS.

Biophysical Principles of Electrical Stimulation of the Brain

In DBS, the IPG creates a stimulation pulse which sends current through the system. A common setting is using a single electrode-contact as the negative pole (cathode), and the IPG as the positive pole (anode). This setting is called monopolar cathodic stimulation. The first DBS systems only allowed using the IPG as an anode, but newer systems enable use of a contact as the anode with the IPG as a cathode, resulting in anodic stimulation. Finally, activating two contacts with different polarities (one contact as an anode and another as a cathode), results in bipolar stimulation which can be used in both older and newer DBS-systems.

Earlier experimental studies found that myelinated axons need several times higher current to be activated using anodic stimulation as compared to cathodic stimulation. However, in the settings of DBS, a recent study on the therapeutic window of different polarities found the scaled difference to be closer to 0.6 with anodic stimulation still needing higher current than cathodic stimulation to achieve similar effects.232,233
The electrical properties of brain tissue are known to be dependent on two main aspects: **conductivity** and **anisotropy**. Conductivity relates to the ability of a material to conduct (disperse) electric current.

Anisotropy relates to the structure and direction of a material, resulting in different conductivity in different directions. In biological material such as grey matter, blood, and CSF, the current spreads equally in all directions as they all lack directionality in their structure. They are **isotropic**. Neuronal fibre tracts (white matter) are densely packed axons which in turn have distinct borders (axon walls) and direction. Therefore, it is several times more difficult for particles to cross the borders than flow along the axons\textsuperscript{214}. Hence, white matter is **anisotropic**.

**FEM: Electric field simulations using the Finite Element Method**

The spatial distribution of the electric field around the electrode can be calculated by solving **field equations**. These equations are used to model the behaviour of electrical fields. However, analytical solutions for field equations only exist for cases when the field is distributed in a simple geometry such as between two metal plates with different electrical charge. As DBS entails distribution of the electric field in three dimensions (x, y, z) in material with different physical properties (electrode and neural tissue), a more complex method is necessary.

The most used method of electric field simulations of DBS is the **Finite Element Method (FEM)**, which deconstructs the calculation of the whole electric field into smaller, **finite**, elements\textsuperscript{225}. In the context of 3D geometry, these elements are designed as tetrahedrons with a mesh-layout (see **Figure 9** on the next page). By solving field equations using specialised computer software in each individual element and combining the results, it is possible to simulate the electric field within this mesh. The equations are solved in the nodes of the tetrahedrons and interpolated over the elements. When applied to DBS, this creates a simulation of the spread of the electric current from the electrode into the surrounding tissue. The equation used is called the steady currents-equation, where the currents to and from a point equal zero (Fig. 9). By assigning values to the different parts of the equation, it is possible to calculate the **electric potential** within the specific element (V = Volt). By comparing the electric potential (V) over a certain distance (mm), the change in electric potential, also called **electric field strength** (V/mm), can be determined.
The necessary input to create the FEM simulations are:

1) Geometry: How large should the modelled field be? What are the properties of the boundaries?
2) The electrode, with metal contacts interspersed plastic insulation, is modelled according to the manufacturer’s technical specifications.
3) Conductivity: Heterogeneous or homogeneous tissue? Anisotropic or isotropic tissue? Peri-electrode glial tissue?
4) Stimulation parameters: One or several contacts? Anodic or cathodic stimulation? Monopolar or bipolar? Voltage or current (mA)? Pulse width? Frequency?

**VNA: Neural activation estimation with Volume of Neural Activation-models**

When the electric field has been simulated, the next step is to apply the effects of electrical stimulation to the surrounding tissue. While the mechanism of DBS remains to be established, the hypothesis used for computer modelling is based on activating axons. This activation of neural tissue (VNA/VTA) has been hypothesized to disrupt pathologic neural activity\textsuperscript{236,237}.

The two most common methods to model axonal activation are the double-cable and single-cable models\textsuperscript{238-240}. These models treat axons as electric circuits and calculate whether a change in extracellular electric potential
affects the voltage-gated ion channels on the axon to such a degree as to trigger an action potential. They depend on several parameters, including DBS settings, and have been found to have similar sensitivity to variations in stimulation amplitude, pulse shape and axon diameter\textsuperscript{236}. Both models have been used to model the effects of DBS and have been implemented in both open-source and commercial software\textsuperscript{241-243}.

These models can be coupled directly with the FEM simulations, making the computer solve millions of equations which creates a need for high processing power and longer time per simulation. One method that lowers the processing demands is the use of electric field magnitude (EF) thresholds to approximate the VNA, called EF \textit{isolevel}. The activation distance from the electrode in single-cable model simulations for a pulse width of 60 µs and with an outer diameter of axons of 3-4 µm has been found to be equivalent of an isolevel of 0.2 V/mm. This diameter represents relatively large axons, with most axons in the brain being smaller. Of the smaller axons, only those located closer to the electrode, where the electric field strength is higher, are activated\textsuperscript{236}. Thus, the visualised border of the field represents the distance from the electrode where large axons are estimated to be activated by the stimulation (see \textbf{Figure 10}).

\textbf{Figure 10.} The equations create a gradient in electric potential around the electrode (black-grey). The border where axons of a certain diameter are estimated to activate based on the electric field strength can be visualised using an EF isolevel. This is a simplification of the concept, and the scaling is not representative of the actual simulations.
By using a specified isolevel based on stimulation settings and surrounding anatomy, it is possible to estimate and visualise VNA by directly using the results of the FEM simulations without running axon-model calculations\textsuperscript{240,244-247}. The benefits of using EF isolevel are less complex and demanding processing, and the possibility to create mm-scaled VNAs in the patient’s own MR-images. On the other hand, the benefits of the axon cable models are that they provide a higher degree of biophysical realism\textsuperscript{248}.

**Group Analysis**

If the goal of VNA modelling is to find optimal/suboptimal stimulation locations, it is necessary to compare patient-specific VNAs and their respective clinical effect with each other. This has been done through visual analysis of mean-effect images, aggregated density maps or using voxel-wise statistics to create \textit{probabilistic stimulation maps (PSM)}\textsuperscript{245-247,249}. There is a clear variability between the methods used, with PSMs having shown the best overall performance in a simulation study\textsuperscript{250}. These methods depend on transferring individual VNAs to a common anatomical domain, either histology-based such as Schaltenbrand-Wahren or Morel’s stereotactic atlas\textsuperscript{136,137}, MRI-based such as the Montreal Neurological Institute (MNI) nLin-aSym 2009b\textsuperscript{251} or a combination of histology and MRI such as the Yelnik-Bardinet atlas\textsuperscript{252}.

There are different methods used to insert VNAs into a group domain, using either coordinates\textsuperscript{253} or MRI-transforms to transfer patient-specific electrode location\textsuperscript{241} and/or VNAs to established atlases\textsuperscript{254} or to a cohort-created space\textsuperscript{255}. The problem with using coordinates is that interindividual differences in anatomy can create significant deviation in location of the active contact in the group domain compared to the individual image\textsuperscript{136,256}. The issues with transforms are the varying accuracy within and between different transformation algorithms\textsuperscript{257}. Regardless, transfer of individual VNAs to established atlases makes for easier comparison between research groups.

While histology-based atlases allow for more detailed delineation of subcortical structures, such as the thalamus and CTT, MRI-atlases benefits from being the same modality as the individual image. The issues with current atlases are that they are either based on very few subjects (Schaltenbrand-Wahren, Yelnik-Bardinet, Morel), have poor 3D-
representation (Schaltenbrand-Wahren), or that they are based on healthy subjects and might not be representative of the anatomy of an elderly, diseased brain (MNI). These issues can be alleviated by creating a cohort-based common anatomical domain using the MR-images of the patients used in a particular VNA-study.

Now that we have established the potential of electric field simulation as a potential tool to analyse and hopefully improve treatment using DBS, it is time to combine the four perspectives presented in this background.

Tremor as part of ET and PD has a negative impact on the patients’ quality of life. These disorders share not only phenotypical but also pathophysiological and anatomical aspects. When medication is insufficient in providing symptomatic relief, PSA-DBS has been found to be a promising treatment for these patients and by targeting the cZi within the PSA, it is possible to perform surgery asleep. By utilising radiological imaging, stimulation parameters and computational software, it is possible to simulate the electric field around the electrode and relate the clinical effects of DBS to the anatomy, thus increasing our understanding of PSA-DBS.

Since we have summarised what we do know about DBS as a treatment for PD and ET, it is time to highlight the gaps of knowledge that served as the basis for the studies in this thesis.
Gaps of Knowledge

- DBS targeting the cZi has been found to improve Parkinsonism but only in non-blinded, non-randomised case series.
- Attempts of elucidating an optimal target within the PSA have neither been conclusive nor taken the stimulation parameters into account.
- There is a paucity of reports on long-term effects of cZi-DBS regarding both PD and ET.
- Asleep surgery has been found to be similar in efficacy as awake surgery regarding STN-DBS for PD but there is a clear lack of reports regarding asleep surgery for ET.

Aims

The aims of the studies in this thesis were:

I) To evaluate, in a single-blinded randomised manner, the effects of bilateral cZi-DBS versus best medical treatment in a group of patients with PD who would fulfil the criteria for bilateral STN-DBS.

II) To map the target area within the PSA concerning the effects of stimulation in relation to the anatomy.

III) To evaluate the long-term effects of unilateral cZi-DBS for PD tremor.

IV) To evaluate the long-term effects of cZi-DBS for ET.

V) To evaluate the effects of awake and asleep surgery in patients operated with cZi-DBS for ET.
Materials and Methods

Study design

The design of the studies of this thesis are summarized in Figure 11.

Figure 11. Study design and number of patients included in the final analyses. Numbers and reasons for drop-out are available in the respective papers.
The design of study I (cZi-DBS vs best medical treatment, BMT) was modelled on the randomised STN-DBS vs BMT trial by Deuschl et al. from 2006. BMT was defined as continuous optimisation of medication by an experienced movement disorders specialist. An unrestricted randomisation was performed by presenting a random number table to a blinded neurologist not involved in the patients’ care. The neurologist pointed at the number table and the numbers of that row were used for randomisation.

### Evaluation

Evaluations were performed at baseline before surgery and at specific follow-ups using similar protocols On/Off medication and stimulation.

In study I, the evaluations were videotaped with the patients wearing head caps. The videos were cut into segments and presented in a randomized order to two blinded assessors. If the score of a subitem differed between the two raters, the particular video segment was reviewed and discussed until an agreed score was established.

In study II and study III, all evaluations were performed non-blinded by the same experienced DBS nurse. In study IV and study V, the evaluations were performed in a similar manner by DBS nurses with the exception that patients with bilateral DBS had two evaluations with one electrode turned on at each evaluation.

### Scales

The Unified Parkinson’s Disease Rating Scale (UPDRS) was used to evaluate the motor symptoms of PD. Parkinsonism was rated using part 3 (UPDRS-III) while dyskinesia and motor fluctuations were evaluated using part 4 (UPDRS-IV).

Health-related quality of life (QoL) was measured using the Parkinson’s Disease Questionnaire-39 (PDQ-39) with summary index to represent overall QoL.

Levodopa-equivalent Daily Dosage (LEDD) was calculated at baseline and at the time-point of each follow up using the conversion table by Tomlinson et al.
The Essential Tremor Rating Scale (ETRS) was used to measure the severity and associated disability of ET\textsuperscript{268}.

Patients

The respective diagnoses (PD/ET) were determined by a senior movement disorder specialist in all patients in accordance with guidelines at the time, with dopamine transporter-imaging as adjunct investigation in some patients\textsuperscript{13,77,269}.

Studies I-II

Patients who would normally be considered for bilateral STN-DBS were eligible for participation in the study. Details regarding inclusion/exclusion criteria can be found in paper I\textsuperscript{259} and are summarised in table 1.

<table>
<thead>
<tr>
<th>Table 1. Inclusion/exclusion criteria for bilateral cZi-DBS</th>
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<tr>
<td><strong>Inclusion</strong></td>
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<tr>
<td>Idiopathic PD</td>
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<tr>
<td>Levodopa response&gt;30%</td>
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<tr>
<td>Disabling motor fluctuations with/without dyskinesias or disabling tremor</td>
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Study III

Patients treated with unilateral cZi-DBS for PD tremor and who completed evaluation at short-term and long-term follow-up were included (one year and >three years after surgery respectively). In our centre, patients not suitable for bilateral STN-DBS and with tremor as a dominant symptom are in selected cases treated with unilateral cZi-DBS. Patients were considered unsuitable for STN-DBS due to factors such as old age, mild-moderate cognitive impairment, or other risk factors for poor outcome such as symptoms ‘non-responsive’ to levodopa.

Study IV-V

In 2004, as part of a prospective, open-label study, the primary DBS-target used for ET was changed from the Vim to the cZi. Data from this study was used in studies IV-V. In 2017, we switched manufacturer and type of DBS
implants. To reduce any effects of different hardware only patients with ET implanted with a constant voltage DBS-system were included in study V.

**Surgical technique**

All patients underwent a stereotactic implantation of DBS electrodes 3387 or 3389 (Medtronic, Minneapolis, MN, USA) using the Leksell frame model G (Elekta Instruments, Linköping, Sweden). Trajectories and targets were planned on preoperative stereotactic T1- and T2-weighted MR images (voxel size 1x1x2mm³, 1.5 T, Philips Achieva, Philips Healthcare, the Netherlands). The target cZi was defined anatomically as lying slightly posteromedial to the visualized posterior tail of the STN on the axial slice showing the maximal diameter of the RN (See section *Surgical Technique* on page 27).

**Awake and Asleep surgery**

After changing from the Vim to the cZi as a primary target for tremor, all implantations were initially performed with the patient awake under local anaesthesia to allow for intraoperative evaluation using macrostimulation. After electrode implantation, the frame was removed, and the patient was put to sleep using general anaesthesia for implantation of the connection cables and IPG. Since 2011, all implantations have been performed under full general anaesthesia starting prior to mounting the stereotactic frame. Implantation of the electrodes, connection cables and IPG (Kinetra/Soletra, Activa SC/PC, Medtronic, Minneapolis, MN, USA) was performed in the same session.

Intraoperative stereotactic or postoperative thin slice CT scans (voxel size 0.6x0.6x1.3mm, Lightspeed, GE Medical Systems, Chicago, IL, USA) were performed and merged with preoperative MRI for visualization of electrode position (MR-CT). No microelectrode recording was performed.
Estimation of stimulation location

The coordinates of the active cathodic contacts were calculated from the MR-CT images in study I. In studies II-III, electric field simulations were performed based on FEM as described by Åstrom et al.\textsuperscript{240}. Both studies generated high-resolution binary VNA. The main differences in simulation and group analyses between study II\textsuperscript{260} and III\textsuperscript{261} are summarized in Table 2 and details of the methods are available in the respective papers.

<table>
<thead>
<tr>
<th>Table 2. Differences in the creation of VNAs in study II-III.</th>
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<tbody>
<tr>
<td><strong>Study II</strong></td>
</tr>
<tr>
<td><strong>Software</strong></td>
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<tr>
<td><strong>Tissue</strong></td>
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<tr>
<td><strong>3D domain</strong></td>
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<tr>
<td><strong>Transform to 3D domain</strong></td>
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<tr>
<td><strong>Group analysis</strong></td>
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</table>

The workflow of study II is found in Figure 12. Patients were divided into response groups based on a review of the literature on the clinical response of STN- and GPi-DBS for PD (see Table 3 for cut offs)\textsuperscript{102,199,258,270-304}.

<table>
<thead>
<tr>
<th>Table 3. Cut-off levels in percentage improvement by stimulation alone in different motor symptoms of PD.</th>
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<tr>
<td><strong>Good</strong></td>
</tr>
<tr>
<td><strong>Total UPDRS-III</strong></td>
</tr>
<tr>
<td><strong>Tremor</strong></td>
</tr>
<tr>
<td><strong>Bradykinesia</strong></td>
</tr>
<tr>
<td><strong>Rigidity</strong></td>
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Conductivity values were assigned by one author, using easily discernible structures (3rd ventricle = CSF, corpus callosum = white matter etc.). 3D models of the STN and RN were created through manual delineation based on the MRI-template.

Study III followed a similar workflow with individual VNAs transformed to a common anatomical domain (See Figure 13).

Figure 12. Overall workflow for patient-specific electric field simulation and group analysis. Top row: Patient-specific workflow. Middle row: group analysis. Bottom row: visualization of the voxel wise statistical test.
In addition to using the anatomical domain, the results of study III were compared side-by-side with two commonly used stereotactic atlases: Schaltenbrand-Wahren's atlas and Morel's atlas\textsuperscript{136,137}.

**Study IV and V**

VNA modelling and analysis have previously been published for a significant part of the cohort of study IV and V\textsuperscript{246,255}. For study IV, the active cathodic contact location was calculated in relation to the MCP. In study V, it was calculated in relation to the MCP and pSTN with the average location \( \pm \) SD in all directions plotted on coronal slices of Morel's atlas.

**Statistical method**

**Sample size**

A power-analysis based on the variability and effect sizes of previous studies on DBS for both PD and ET would have been appropriate to calculate sample size. Regarding study I, a power-analysis with an alpha = 0.05, 90\% power and a 40\% decrease in total UPDRS-III would necessitate 20 patients based on previous studies.

Due to practical reasons and inherent treatment population-based constraints, studies III-V utilised convenience samples of patients operated at the DBS-unit at Umeå University Hospital.
Statistical tests

- Two-tailed dependent/independent t-tests or ANOVA for repeated measurements were used for continuous variables (two or more measurements respectively).
- Wilcoxon’s signed rank test and Friedman’s test were used for within-group analysis of non-parametric variables (two or more interdependent groups respectively).
- Mann-Whitney U-test and Kruskal-Wallis test were used for between-group analyses of non-parametric variables (two or more independent groups respectively).
- Statistical analysis of the binary VNAs in correlation to the clinical outcome was made using a double-sided Wilcoxon’s rank sum test.
- Differences between distributions in categorical variables in study IV-V were assessed using Pearson's chi-square test.

A p-value <0.05 was considered statistically significant. In study II-III and study V, the Bonferroni method was used to correct for multiple comparisons of rater assessments.

Ethical Considerations

All studies in this thesis were approved by the Ethical Committee of Umeå University and informed consent was obtained from participants according to the Declaration of Helsinki (version 2008).
Results

cZi-DBS for Parkinson’s disease (Studies I-III)

Effects on motor symptoms

Bilateral cZi-DBS vs BMT

There were no statistically significant differences between the BMT group and the cZi-DBS group at baseline regarding age, disease duration, LEDD, or UPDRS-III scores On/Off medication (Table 4).

Scores are presented as mean ± SD Off medication unless otherwise specified. Total UPDRS-III scores were better in the cZi-DBS group On stimulation compared to the BMT group (19.5 ± 7.8 vs 37.2 ± 12.2). On medication, there were no statistically significant differences in total UPDRS-III scores between the two groups (18.5 ± 12.4 vs 21.8 ± 13.4). Tremor and bradykinesia scores were lower in the cZi-DBS group On stimulation, Off medication compared with the medical group Off medication (6.9 ± 5.6 vs 0.4 ± 0.5 and 14.3 ± 6.6 vs 9.7 ± 5 respectively, p<0.02).

There were no differences between the groups in speech, axial symptoms, dyskinesia, fluctuations or in LEDD at six-month follow-up.

Table 4. Patients’ characteristics in medical group and surgical group at baseline. Values represent mean ± SD. ns=not significant, p>0.05

<table>
<thead>
<tr>
<th></th>
<th>BMT</th>
<th>cZi-DBS</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>10</td>
<td>9</td>
<td>ns</td>
</tr>
<tr>
<td>Male/female</td>
<td>8 /2</td>
<td>7 /2</td>
<td>ns</td>
</tr>
<tr>
<td>Age (years)</td>
<td>60.9 ± 9.2</td>
<td>57 ± 11.4</td>
<td>ns</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>10.3 ± 5.6</td>
<td>6.4 ± 3</td>
<td>ns</td>
</tr>
<tr>
<td>LEDD at baseline (mg)</td>
<td>1043 ± 516</td>
<td>1376 ± 883</td>
<td>ns</td>
</tr>
<tr>
<td>UPDRS-III at baseline Off medication</td>
<td>42.4 ± 14.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>33.2 ± 11.4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>ns</td>
</tr>
<tr>
<td>UPDRS-III at baseline On medication</td>
<td>20.6 ± 11.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>19.4 ± 12.5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>ns</td>
</tr>
</tbody>
</table>

<sup>a</sup> within group, p=0.001.  <sup>b</sup> within group, p=0.01
**Results of Bilateral cZi-DBS on Parkinsonism**

In the 15 patients with bilateral cZi-DBS who completed one-year evaluations, the mean age at surgery was 58.6 ± 9.7 years with a mean duration since PD diagnosis of 6.5 ± 2.6 years.

Scores are presented as median (interquartile range, IQR) Off medication unless stated otherwise. **Table 5** shows the sub-scores of UPDRS-III at baseline and one-year follow-up.

**Table 5.** UPDRS-III at baseline and at one-year follow-up. Expressed as median (IQR)

<table>
<thead>
<tr>
<th>UPDRS-III</th>
<th>Baseline</th>
<th>One-year follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Max. score</td>
<td>Off med</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>108</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(20)</td>
</tr>
<tr>
<td>Axial</td>
<td>32</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(3)</td>
</tr>
<tr>
<td>Tremor</td>
<td>28</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(10)</td>
</tr>
<tr>
<td>R rigidity</td>
<td>20</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(4)</td>
</tr>
<tr>
<td>Bradykinesia</td>
<td>32</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(5)</td>
</tr>
<tr>
<td>Dyskinesia</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(3)</td>
</tr>
<tr>
<td>LEDD (mg)</td>
<td></td>
<td>1227</td>
</tr>
</tbody>
</table>

a) p≤0.05 vs baseline Off medication
b) p≤0.05 vs Off medication/Off stimulation at the same follow-up
c) p≤0.05 vs baseline On medication
d) p≤0.05 vs On medication/Off stimulation at the same follow-up
e) p≤0.05 vs Off medication/On stimulation at the same follow-up

Total UPDRS-III scores were improved by stimulation alone in comparison to baseline and in comparison to Off stimulation at the same follow-up in both blinded (study I) and non-blinded evaluations (48-50% at one-year follow-up in study II, p<0.005). Stimulation and medication combined led to further improvement compared to stimulation alone (38%, p<0.001).

Regarding efficacy profile, median tremor score was improved by 90% (p<0.0001), rigidity by 29% (p<0.005) and bradykinesia by 25% (p<0.01) on stimulation at one-year follow-up compared to baseline. The effect was slightly larger when compared to Off stimulation at the same follow-up time point.
No statistically significant changes were seen concerning axial scores, dyskinesia, motor fluctuations or LEDD at one-year follow-up compared with baseline.

**Effects on Quality of Life**

*Bilateral cZi-DBS vs BMT*

Patients in the BMT group and the cZi-DBS group both reported improved QoL according to the PDQ-39 summary index at 6-month follow-up compared to baseline (24%, \( p=0.028 \) and 36%, \( p=0.038 \) respectively). There was no statistically significant difference in PDQ-39 summary index score neither at baseline nor at 6 months.

Regarding sub-domains, only the cZi-DBS group reported significant improvement at 6 months, in domains “ADL” and “Stigma” (-17.6 points and -22.9 points in mean scores respectively, \( p<0.03 \)). At baseline, as well as at 6 months, the cZi-DBS group reported better scores than the BMT group on the dimension “Emotion” (8.8 ± 6.7 vs 24.5 ± 15.4 at follow-up).

*Results of Bilateral cZi-DBS on Quality of Life*

At one-year follow-up bilateral cZi-DBS showed a maintained statistically significant improvement compared to baseline regarding “ADL”, which improved from a median of 16.7 (29.2) to 12.5 points (33.3, \( p<0.03 \)), and “Stigma” from 25 (25.3) to 6.3 (25, \( p<0.01 \)). However, the sub-domain “Communication” worsened from 0 (8.3) to 16.7 points (16.7, \( p<0.01 \)). There was a trend towards better PDQ-39 summary index at one-year but did not reach statistical significance (from 17.8 to 13.2).
Long-term effects of Unilateral cZi-DBS for PD

In study III, the mean age at surgery was 67 ± 5.5, mean LEDD was 670 ± 407mg at baseline, three of 13 patients underwent surgery asleep, and three patients had <30% improvement on L-dopa challenge before surgery. Other details regarding characteristics are available in paper III261. Patients were evaluated at short-term follow-up at a mean of 14 ± 5 months and at long-term follow-up 62 ± 17 months (5.2 ± 1.4 years) after surgery.

There were no significant changes in Off medication/Off stimulation scores between short- and long-term follow-up (see table 3 in paper III). The following scores are presented as median (% change) Off medication unless otherwise stated.

Total UPDRS-III scores were reduced from 42 Off stimulation to 28 (33%) with stimulation at short-term and from 45 to 35 (22%) at long-term follow-up in comparison to Off stimulation at the same follow-up time point (p≤0.001). The corresponding improvements for contralateral UPDRS-III scores were 50% and 43%, respectively (p≤0.001).

Contralateral tremor scores were improved from 8 to 1 with stimulation alone both at short-term and long-term follow-up (88%, p≤0.001). The reduction in tremor was also significant when compared to baseline (p≤0.05). Stimulation combined with medication abolished contralateral tremor in seven patients at long-term follow-up, with three patients having a score of 1 point, one patient with 3 points, and one patient with a score of 4 points respectively. There was no apparent relation between follow-up time and degree of tremor reduction (table 2 in paper III261).

Contralateral bradykinesia scores were reduced from 10 to 6 by stimulation alone at short-term and from 10 to 8 at long-term (40 and 20% respectively, p≤0.005).

Contralateral rigidity scores were reduced by 33% at short-term evaluation but did not survive Bonferroni-correction (p=0.022) and was not significantly reduced at long-term follow-up.

LEDD was increased by a mean of 337mg ± 88mg from short-term to long-term follow-up (p≤0.01).
cZi-DBS for Essential Tremor (Studies IV-V)

One-year results

In study V, a total of 102 electrodes in 86 patients were available for one-year analysis, with 35 patients (5 bilateral) having undergone electrode implantation awake and 51 patients (11 bilateral) asleep. Details of patient characteristics and specific subgroups are found in the manuscript\textsuperscript{263} and summarised in \textbf{Table 6}.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|}
\hline
\textbf{Female} & \textbf{Age-at-onset} & \textbf{Age-at-surgery} & \textbf{Disease duration} & \textbf{Heredity} & \textbf{Alcohol response} \\
\textbf{Male} & & & & \textbf{Yes/No/Unknown} & \textbf{Yes/No/Unknown} \\
\hline
34/52 & 36.2 ± 19.2 & 65.7 ± 1.6 & 29.2 ± 18.2 & 60/22/4 & 55/6/25 \\
\hline
\end{tabular}
\caption{Patient characteristics of all patients in study V. Expressed in numbers or mean ± SD (min-max)}
\end{table}

The following results are presented as median (IQR) unless stated otherwise. Total ETRS scores were reduced from 51 (22) points at baseline to 19 (14) On stimulation at one-year follow-up ($p<0.0001$). The median individual improvement in percentage was 61%. A similar improvement was seen comparing Off stimulation to On stimulation at follow-up. Contralateral arm tremor scores (items 5/6) were improved from 6 (3) at baseline to 0 (0) On stimulation at follow-up ($p<0.0001$). Specifically, 96 evaluated arms had a score of 0-1 (78 and 18), 4 arms had 2 points and 2 arms had 3 points in contralateral arm tremor (all forms of tremor). Regarding action tremor, only one patient had a score >1 (2 points).

A compound score of contralateral arm tremor and hand function (items 5/6 and 11-14) was significantly improved from 18 (9) at baseline to 3 (3) On stimulation at follow-up while ADL score (items 15-21) improved from 13.5 (5) to 2 (4) ($p<0.0001$). A similar improvement was seen between Off and On stimulation.

Long-term effects of cZi-DBS for ET

Background characteristics of participants (patients followed for 10 years) and dropouts (patients lost to 10-year follow-up prior to the study cut off) of study IV are summarised in \textbf{Table 7} with details available in paper IV\textsuperscript{262}. 

53
Table 7. Background characteristics of participants and dropouts

<table>
<thead>
<tr>
<th></th>
<th>Participants</th>
<th>Dropouts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female/male</td>
<td>9/8</td>
<td>6/11</td>
</tr>
<tr>
<td>Age at disease onset</td>
<td>43.1 ± 19.6</td>
<td>38.6 ± 22.2</td>
</tr>
<tr>
<td>Age at surgery</td>
<td>65 ± 8.9</td>
<td>65.8 ± 15.9</td>
</tr>
<tr>
<td>Disease duration</td>
<td>21.4 ± 15.4</td>
<td>27.2 ± 18.6</td>
</tr>
<tr>
<td>Unilateral/bilateral</td>
<td>14/3</td>
<td>15/2</td>
</tr>
</tbody>
</table>

There were no statistically significant differences at baseline between the 10-year dropouts and participants. However, dropouts had higher total ETRS scores than participants at the follow-up time-points 1 year and 3-5 years after surgery. To avoid overestimation of the effect of cZi-DBS over time, the analyses in the following sections include all patients evaluated at each respective time point: 34 individuals at baseline, 33, 30 and 17 individuals at year 1, 3-5 and 10 respectively.

**Overall effects on tremor during the first decade after surgery**

Stimulation resulted in a significant improvement in total ETRS scores (66.4%), tremor scores (70.7%) and hand function scores (56.3%) at one-year follow-up after surgery compared to preoperative baseline scores. A significant improvement versus baseline was maintained over time, but reduced to 50.8%, 55.8% and 44.3%, respectively, at 10 years after surgery (Figure 14). The difference between mean scores On and Off stimulation remained statistically significant at each time point.

**Symptom progression over 10 years**

Total ETRS scores Off stimulation remained largely unchanged over 10 years compared to baseline. This was further analysed in unilaterally implanted patients, where arm tremor and hand function (items 11-14) were unchanged at 10 years on both sides Off stimulation, and on the ipsilateral side On stimulation. In contrast, contralateral arm tremor scores and hand function scores On stimulation deteriorated at 10 years.
Long-term differences between unilateral and bilateral cZi-DBS

There were 29 unilaterally and 5 bilaterally implanted patients. As illustrated in Figure 15 on the next page, the treatment effect was stronger in bilateral compared to unilateral patients, while the ETRS scores were worse Off stimulation. The effect of stimulation diminished over the years in both groups, although more in bilateral patients.
Patient characteristics of study V are illustrated in Figure 16. There were no statistically significant differences in age at disease onset, age at surgery and disease duration between patients that underwent awake and patients that underwent asleep surgery. There was a significant difference in procedure time (skin-to-skin, implantation of electrode, connection cables and IPG) between groups with unilateral asleep surgery being 1 hour and 39 minutes shorter than awake surgery on average (95% CI 65.5-131.6 minutes). The difference was greater regarding bilateral implantations with a median of 5 hours and 31 minutes for awake surgery and 2 hours and 53 minutes for asleep surgery (p<0.01).
Baseline and Off stimulation

Specifically comparing the awake patients with the asleep patients revealed that at baseline, contralateral arm tremor scores were slightly higher in the awake group ($p=0.01$). Neither total ETRS, Part A (items 1-9), hand function, nor ADL-scores were significantly different between the groups at baseline.

Total ETRS scores were worse Off stimulation at one-year follow-up compared with baseline in the asleep group (56.5 vs 50.5, $p<0.005$). This was reflected mainly by worse functional scores at follow-up (Hand function and ADL). There was no significant difference in ETRS-scores in the awake group between baseline and follow-up Off stimulation. Comparing scores at follow-up, contralateral hand function ($p<0.005$), and ADL ($p<0.005$) were worse in the asleep group than the awake group Off stimulation.

Effect of stimulation

Unilateral stimulation significantly improved total ETRS in comparison to baseline by a median of 29.5 points in the awake and 31.5 points in the asleep group (61% and $p<0.001$ within groups, non-significant between groups). Contralateral arm tremor and hand function improved by stimulation in both groups, both in comparison to baseline and to Off stimulation ($p<0.001$).
The scores on stimulation were similar in both groups regarding total ETRS, Part A, and ADL with a trend towards better contralateral arm tremor and hand function in the awake group (Figure 17, \( p=0.04 \)).

By defining a poor response as <40% improvement on total ETRS (-1 SD) between baseline and at follow-up on stimulation, there was three evaluated hemibodies in the awake group with a poor response and eight in the asleep group (non-significant, \( p>0.05 \)).

**Figure 17.** Boxplots of Part A, contralateral arm tremor and function and ADL in both groups preoperatively and On/Off stimulation. \( x = \) mean. Striped = awake.
Stimulation parameters and location

**Figure 18** shows the fused MRI-CT images at the depth of the active cathodic contact in each hemisphere with cZi-DBS from study I. The active contacts were in the PSA in all patients. The median amplitude at one-year follow-up was 2.45 V (0.6, IQR), pulse width 60 µs (7.5) and frequency 145 Hz(30). The estimated volume affected by the stimulation was 100 mm$^3$ (interquartile range: 71, min-max: 41-283) one year after surgery.

**Figure 18.** Fused axial CT-MRI scans at the level of the active contact. Coordinates are given in relation to the midcomissural point (MCP).
**Improvement maps of Parkinsonism (Study II)**

Regarding total UPDRS-III, the distribution of the anatomical improvement maps was mostly overlapping between good/moderate/poor responders. This was also the case regarding the different sub-scores apart from a tendency towards a more superior location among good responders on tremor (See **Figure 19**). The voxel-wise statistical test did not reveal an area where the effect could be predicted since only a few voxels showed statistical significance ($p<0.05$).

**Figure 19.** Improvement maps based on total UPDRS-III and sub-scores for axial, tremor, rigidity, and akinesia. The improvement maps are overlaid on axial and coronal MRI slices and to the right a 3D representation in relation to the STN and RN (purple).
**Long-term changes in stimulation for Parkinsonian tremor (Study III)**

The stimulation parameters and mean contact coordinates in study III can be found in paper III. Pulse effective voltage (PEV) was used as a measurement of stimulation strength ($\sqrt{U^2 \times pps \times pw}$), where $U$=voltage (V), $pps$=pulses per second (Hz) and $pw$=pulse width (µs).

There were no statistically significant differences in stimulation parameters or contact location between short-term and long-term follow-up. The location of the active cathodes and 3D models of the thresholded overlapping VNAs are visualised in Figure 20 and the side-by-side comparison to stereotactic atlases are available in paper III. The field extends along the mean trajectory of the lead and is concentrated in the PSA just inferior to the VL thalamus.

The simulation fields were virtually completely overlapping between the short-term and long-term follow-up.

---

**Figure 20. Posterolateral view of the 3D domain.**

A) The contact locations.

B-C) Aggregated VNAs at short-term (light blue) and long-term (dark blue) follow up in relation to the STN (green) and RN (red).
**Long-term changes in stimulation for Essential Tremor (Study IV)**
A minor increase in the energy delivered was seen from the start around week six to year 1, but no further increase was seen 10 years after surgery. Sixteen of the 34 patients underwent a single IPG replacement due to battery depletion during the follow-up period.

**Differences in stimulation between awake and asleep surgery (Study V)**
The mean location of the active cathodic contact of the whole cohort was located 2.1 ± 1.3mm medial, 0.2 ± 1.2mm anterior and 2.6 ± 1.4mm superior to the pSTN. The mean angles were 27.9 ± 7.1 degrees and 19.2 ± 4.9 degrees in the anterior-posterior and medial-lateral direction relative to coronal and sagittal midlines respectively. The active contacts were located more superior and more lateral in the asleep group than the awake group. The mean differences between the groups were 1.2 ± 0.4mm (95% CI 0.4-2.0) and 0.7 ± 0.3mm (95% CI 0.2-1.2) regarding depth and laterality respectively. The only statistically significant difference in MCP-coordinates concerned depth.

Regarding stimulation parameters, more patients in the awake group used bipolar settings than in the asleep group (10 vs 2). In addition, the asleep group had lower amplitude, frequency and PEV than the awake group at one-year follow-up ($p<0.009$). The mean difference was 0.37 ± 0.14V (95% CI 0.1-0.6), 15.1 ± 3.6Hz (95% CI 7.9-22.3) and 0.05 ± 0.014V (95% CI 0.022-0.08) regarding amplitude, frequency and PEV respectively. Mean stimulation parameters are found in table 8.

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Awake</th>
<th>Asleep</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amplitude (V)</strong></td>
<td>1.99 ± 0.65</td>
<td>2.22 ± 0.74</td>
<td>1.85 ± 0.54</td>
</tr>
<tr>
<td><strong>Pulse width (µs)</strong></td>
<td>62.7 ± 10.4</td>
<td>64.5 ± 12.8</td>
<td>61.5 ± 8.5</td>
</tr>
<tr>
<td><strong>Frequency (Hz)</strong></td>
<td>155.2 ± 18.2</td>
<td>164.4 ± 19.6</td>
<td>149.3 ± 14.6</td>
</tr>
<tr>
<td><strong>PEV</strong></td>
<td>0.196 ± 0.07</td>
<td>0.226 ± 0.077</td>
<td>0.176 ± 0.054</td>
</tr>
</tbody>
</table>

Table 8. Stimulation parameters at one-year follow-up expressed in mean ± SD
Adverse events

There were no intracranial haemorrhages or skin erosions in any of the studies. Of the patients with PD, one patient suffered a serious perioperative adverse event (one electrode extirpation due to infection).

Of the patients with ET, three patients suffered serious adverse events (pneumonia and lacunar infarction, electrode extirpation due to inflammation, pulmonary embolism). There were slightly more perioperative adverse events in awake surgery than asleep surgery (12 in 35 patients vs 7 in 51 patients).

Some patients experienced transient symptoms after surgery, such as headache, gait or speech disturbance, but these were in most cases mild and completely resolved 1 month after surgery. Eight patients with ET experienced mild speech or gait disturbance lasting up to one year after surgery which were attributed as microlesional side effects.

Stimulation-induced side-effects at follow-ups were noted and commonly concerned gait/balance and speech. These cases were mild, and it was possible to adjust parameters to reduce the side effects without major deterioration in efficacy in all but a few patients. Some patients did not want to decrease stimulation parameters despite side effects. Temporary stimulation-induced side effects seen during the optimization of stimulation parameters are not reported in this dissertation.

Clinically relevant habituation/upper limb ataxia necessitating multiple changes of the stimulation parameters were noted in 16 treated hemibodies with ET during the first year, with some experiencing both problems. Over 10 years, six patients developed these issues after a mean time of 4 years (range 0.5–10 years) after surgery.

No patient with PD experienced similar habituation or ataxia.
Discussion

The studies of this thesis found that DBS targeting the cZi markedly improved tremor in PD and ET. cZi-DBS had a modest effect on bradykinesia and rigidity, and improved the quality of life of patients with PD. The improvement on tremor was retained over time when evaluated at a mean of 5 years after surgery for PD and 10 years after surgery for ET. Although some deterioration was seen regarding cZi-DBS for ET, there was still a considerable improvement at long-term follow-up. Further, visual anatomical targeting of the cZi enabled asleep surgery where a seemingly similar degree of improvement was seen as in awake surgery for ET.

Finally, the simulated VNAs and active contacts used to achieve these effects were consistently found to be concentrated in a region below the Vim, medial and above the posterior STN. The principal parts of this region are comprised of the cZi and the CTT, hypothesised to be a major part of the pathophysiology of both PD tremor and ET.

This thesis contributes to the existing literature by reporting the first randomised, blinded study of cZi-DBS for PD and the first very long-term results of cZi-DBS for ET. Further, it adds to the very limited knowledge about long-term cZi-DBS for PD and asleep DBS for ET. Finally, it provides the first VNA analysis of cZi-DBS for PD in relation to the clinical effects.

The target

In the following discussion, PSA-DBS will refer to all studies of DBS in the PSA regardless of which structure within the PSA used as the target. cZi-DBS will refer to studies using our targeting method.

The title of this dissertation is worded in a way to reflect one of the major aspects of why I decided to call it cZi-DBS instead of PSA-DBS. In fact, these terms have been used interchangeably in published papers from the DBS-unit in Umeå since 2009, including studies in this thesis.

1) The wording “targeting the cZi” was chosen over “DBS in/of the cZi” to clarify that it is not necessarily stimulation of the cZi itself that causes symptomatic relief but merely that it reflects the anatomical landmark we use as a stereotactic target.
II) Specifying cZi as a target was chosen over “PSA-DBS” to separate the targeting method from alternative, both current and future, methods of stimulating structures in the PSA, such as targeting the CTT or PTT.

As none of the studies in this thesis directly compare cZi to other targets, the following discussion also comes with two important caveats:

I) As previously written, STN- and Vim-DBS do not always reflect the precise structure receiving stimulation, and the same is the case for cZi-DBS. Thus, the results of these studies should firstly be connected to the targeting method used, not the anatomical structure through which stimulation achieves its effects. A more anatomical discussion can be seen in section What...?

II) Any indirect comparison of results between studies are insufficient to truly elucidate any similarities or differences. To do so, a randomised, blinded study comparing targets head-to-head is needed. Nevertheless, some insight can still be gleaned from putting the results in perspective to each other.

DBS targeting the cZi for Parkinson’s disease

Effects on Parkinsonism

In study I, the blinded evaluation showed that stimulation alone improved total UPDRS-III scores by a mean of 42% and 45% at 6-month follow-up in comparison to baseline Off medication and 6-month Off stimulation/Off medication. The percentage of improvement was similar to that reported in blinded and/or randomised trials of bilateral STN- and GPi-DBS, ranging between 25-50%. In our study, the cZi-DBS group On stimulation had significantly lower total UPDRS-III scores than the BMT-group Off medication but not On medication. This might be due to the small sample size, rendering small effect sizes to be underpowered, or that cZi-DBS has a similar but not higher improvement than levodopa. Of note, the differences between STN- and GPi-DBS and BMT On medication is often several times smaller than Off medication comparisons.

The open-label one-year evaluation in study II showed an undiminished median improvement of 48% and 50% on total UPDRS-III by bilateral cZi-
DBS in comparison to baseline and to Off stimulation. To establish non-arbitrary responder groups for analysis of the improvement of cZi-DBS with regards to anatomy, I conducted a search of the literature regarding improvement of STN-/GPi-DBS for PD. In 38 studies, there was a 25-75% improvement of total UPDRS-III in open-label studies on bilateral STN- and GPI-DBS with a median of approximately 50%. Interestingly, a formal meta-analysis of open-label studies later found an estimated pooled improvement of 50.5% on total UPDRS-III by STN-DBS (38 studies) and 29.8% by GPI-DBS (5 studies).307

A comparison between our results and other studies of DBS using structures in the PSA as a target for PD is made difficult by several factors: a propensity for unilateral evaluation, differences in disease duration and severity, phenotypical presentation, targeting method and actual location of the electrode contacts and field of stimulation206,208-211,308-312.

The results of bilateral stimulation of PSA-DBS for PD have only been reported in 22 patients across 4 previous studies, with one possible duplicate of 5 patients208,211,308,310. Only one study reported total UPDRS-III scores in 5 patients, with an improvement of approximately 65%208. The other PSA studies focused on specific subitems of UPDRS-III, where bilateral stimulation showed similar results as unilateral stimulation. The mean follow-up periods in these studies are between 6-24 months, with only a few patients being followed beyond 2 years311.

Regarding the cardinal motor symptoms of PD, we found that cZi-DBS had a pronounced effect on tremor (88-93%), whilst modest on bradykinesia (25-40%) and rigidity (29-33%) both for unilateral and bilateral stimulation up to one year after surgery (study I-III). These results contrast with previous studies of PSA-DBS. While contralateral tremor was likewise much improved (75-93%), other studies have reported considerable improvement also for contralateral bradykinesia (46-75%) and rigidity (45-94%)208-211,308,310,311.

One reason to the discrepancy to other PSA studies could be differences in assessment. The group in Mexico, led by F. Velasco, wrote in their first paper from 2001 "Rigidity as judged by the cogwheel sign was also significantly reduced, although it was more difficult to assess". This calls into question what symptom was actually being assessed since in the UPDRS-III manual for evaluation, cogwheeling is to be ignored when
evaluating rigidity as this is easily confounded (and might be caused) by the presence of tremor\textsuperscript{77,313}. Indeed, there are known issues with interrater variability of clinical evaluation of motor symptoms, especially regarding rigidity\textsuperscript{265,314}.

Regarding bradykinesia, the absolute point-reduction is more similar to some PSA studies than relative improvement (%) but one could argue that there is still a noticeable difference in effect size. Speculatively, the patients in other studies could have a more prominent expectancy effect, known to affect PD patients’ performance on motor tasks as well as the effects of DBS, more so for bradykinesia than tremor\textsuperscript{315-319}. Additionally, the possibility of rater-bias underscores the importance of blinded clinical evaluations, especially regarding novel brain targets. Finally, differences in the targeting method could influence which anatomical structures were affected by the electrical current and will be discussed later (see “What...?”). Whether these or other aspects such as patient selection, stimulation regime or interindividual variations of fibre tracts are responsible for the discrepancy in effects is not possible to determine from the current studies.

Finally, cZi-DBS did not have a clear beneficial effect on axial symptoms or speech-related scores.

Regarding the effects of bilateral STN-/GPi-DBS on cardinal symptoms, only some of the randomised/blinded trials provide conclusive reports of specific symptoms. Available results from these trials showed an unweighted mean improvement (range) of bilateral STN-/GPi-DBS on tremor 71\% (49-100\%), bradykinesia 34\% (20-52\%), rigidity of 44\% (25-63\%)\textsuperscript{270,302,320-321}. Expanding the comparison to include smaller open-label non-randomised, non-blinded studies, the median range of improvement on tremor increases to 78-81\%, bradykinesia to 45-52\% and rigidity to 56-63\%\textsuperscript{102,199,258,270-304,324,325}.

**Long-term effects of cZi-DBS on Parkinsonian tremor**

Study III found that DBS targeting the cZi reduced contralateral PD tremor score from a median of 8 points to 1 point (88\%) with stimulation alone at one-year follow-up with no decline in efficacy after a mean of 5 years after surgery.
Only one other study has evaluated the effects of PSA-DBS for PD beyond three years after surgery\(^\text{311}\). Eight patients with unilateral Raprl-DBS were followed for 48 months. The median contralateral tremor score was reduced from 5.9 at baseline to 2.2 at last follow-up, (approximately 63% tremor-reduction). Half of the long-term patients were classified as having excellent effect on tremor (90-100%), whilst half had “sub-optimal” effect on tremor (33%-75%) but seemed to have had an improved effect after optimization. According to the boxplot, there seemed to be a lower median score with less variance when compared with longer-term follow-ups but no statistical testing between specific time points was performed.

While there is no comparative study between PSA- and Vim-DBS, there have been some studies on the long-term effect of unilateral Vim-DBS for PD tremor. These found a tremor reduction between 55-82% up to 4-6.6 years after surgery\(^\text{187,227,229,326,327}\). The largest multicentre study by Hariz et al. found a mean improvement of 82% on contralateral tremor scores in 30 patients with PD 6.6 years after surgery\(^\text{187}\). Notably, the patients showed a significant spontaneous reduction of tremor over time with a tremor score of 8.4 at baseline before surgery and 3.3 at last follow-up Off stimulation, as is sometimes the case in patients with PD. In contrast, the tremor scores in our study remained high in the off condition even at long-term follow-up.

Regarding unilateral STN-DBS for PD tremor, only a few studies have specified the improvement of the different motor symptoms. The follow up was usually short, between 3-23 months, and the preoperative tremor score modest (mean 2.3 points)\(^\text{328-331}\). Nevertheless, the improvement was 72-86%, 22-46% and 39-66% on tremor, bradykinesia, and rigidity, respectively. Recently, Liang et al. reported on the long-term effect of unilateral STN-DBS in 23 patients with asymmetrical PD\(^\text{332}\). Five years after surgery they noted a decrease of contralateral tremor by 82%, with a non-significant effect on action tremor, and an improvement on rigidity by 81% and bradykinesia by 58%.

In study III, rigidity was not clearly alleviated by unilateral stimulation at long-term follow-up. This could mean that the reduction in rigidity in study I-II might be due to regression toward the mean or an expectancy effect. The consistent beneficial results of PSA-DBS on rigidity in other studies supports the notion of at least some effect of cZi-DBS on rigidity, albeit small. Whether this is the case or that the results of study III are due to a
Discussion/DBS targeting the cZi for Parkinson's disease

diminished effect of stimulation on rigidity over time or a small effect size combined with a small sample would have to be evaluated in future larger studies. An alternative explanation would be that the effects of cZi-DBS on rigidity is dependent on levodopa-responsiveness (as is the case with STN-DBS and Parkinsonism). This notion is supported by the fact that three patients had <30% improvement on levodopa prior to surgery and the fact that contralateral rigidity was not significantly reduced by levodopa alone at long-term follow-up.

As such, the effect of cZi-DBS on PD tremor was prominent while the effect on bradykinesia and rigidity was on the lower end of the spectrum of results seen in other PSA-DBS studies as well as the results seen in the literature of bilateral STN/GPi-DBS.

Effects on motor complications and medication in PD

Regarding dyskinesia and motor fluctuations, STN- and GPi-DBS are known to significantly reduce “time off” and dyskinesia severity across different methods of measurement. In contrast, our study found no difference within or between the BMT group and cZi-DBS group regarding these symptoms as measured by UPDRS-IV. This might be a floor effect considering the relative sparsity and severity of these symptoms in our cohort. As an example, subitem 32 of UPDRS-IV is used as a measurement of the relative amount of time with troubling dyskinesia each day (percentage). Of the 15 patients concluding one-year follow-up, two reported dyskinesia 1-25%/day, three patients 26-50% and one patient 76-100%/day at baseline. At one-year follow-up four had improved dyskinesia whilst two had an unchanged score compared to baseline. One additional patient reporting no dyskinesia at baseline but reported 1-25%/day at one-year follow-up.

Only two of the surveyed PSA-DBS studies have reported outcome on dyskinesia. Plaha et al. found a mean reduction of 56% (21-91% CI) using the clinical dyskinesia rating scale while Velasco et al. (2016) reported that in nine patients, dyskinesia and motor fluctuations were diminished or had disappeared.

In contrast to STN-DBS, but similar to GPi- and Vim-DBS, LEDD was not significantly reduced by bilateral cZi-DBS at neither 6-months nor one-year follow-up. The same was seen regarding unilateral cZi-DBS at short-term
follow-up but with a significant increase in LEDD between baseline and long-term follow-up. During the same time, total UPDRS-III Off medication worsened, mainly concerning ipsilateral symptoms. Therefore, the increase in medication can at least partly be attributed to worsening of ipsilateral symptoms. The change in this study was in the same range as seen in most of the long-term studies on unilateral Vim-DBS for PD tremor, apart from the multicentre study by Hariz et al. which reported no change.

Effects on Quality of Life in PD
Both the BMT group and the cZi-DBS group reported improvement in QoL as measured by PDQ-39. The mean summary index (PDQ-39 SI) was reduced by 6 points (24%) in the BMT group and 8 points (36%) in the DBS group at six months compared with baseline. These changes could be due to a regression to the mean as there was no clear difference between the groups. However, the two domains ADL and Stigma showed significant change only in the surgical group at six-month follow-up and were also improved in the whole cohort at one-year follow-up in comparison to baseline. Other reasons for improvement in PDQ-39 SI could be due to adjustments in medical regime despite minimal effects on LEDD and UPDRS-III (in the BMT group), the Hawthorne effect, or placebo and expectation effects known to be especially strong in PD.

At one-year follow-up PDQ-39 SI was not significantly improved on the group-level, which, besides the fact that there was no improvement in QoL, could have been due to the small sample size or the reported worsening in Communication. One way to evaluate individual relevant improvement is the reliable change index which has been used in studies on STN-DBS. Based on the results in study II, this would result in 40% of patients having a relevant improvement on QoL, 53% reporting no change and one patient rating worse QoL at one-year follow-up. This is in line with studies on QoL after STN-DBS which have found between 32%-57% of patients receiving STN-DBS to have a relevant improvement on PDQ-39 SI.

This reflects what we see in the clinic, with some patients rating an improvement in QoL, while others do not, despite improvement in motor scores or even in perceived improvement in QoL. This, and the fact that ADL and Stigma were improved, is supported by what patients in our clinic have reported during in-depth interviews where a clear majority (83%)
reports a moderate to marked impact of DBS on life. In these interviews, the main life areas limited by PD were ADL and social withdrawal/isolation with tremor being a very pervasive symptom and impacted several aspects of the patients’ daily life.

The fact that tremor specifically impacts ADL and Stigma is not unknown. A recent review covered the aspects of Stigma in PD, highlighting the stress, shame, and loneliness people with PD experience. Especially visible symptoms, such as tremor, lead to greater stigmatization and social isolation. As such, the fact that cZi-DBS was found to significantly improve tremor, support the notion that these patients have a resulting benefit on, at least parts of, their quality of life.

Regarding the lower scores on Communication, this is in accordance with our previous study showing a worsening in spontaneous speech intelligibility in three out of 11 PD patients with bilateral cZi-DBS at one year after surgery. While neuropsychological testing of the current cohort did not find a decline in verbal fluency, as seen in STN- and GPi-DBS, there was a negative trend regarding phonemic and category fluency. This might, together with dysarthria, have contributed to the worsened communication scores of the PDQ-39. Notably, the scoring on PDQ-39 domains in general, but especially regarding Communication, was lower in our cohort both at baseline and at follow-up in comparison to the STN/GPi-trials using QoL-measurements as outcome.

The improvement on QoL in our cohort was similar to the STN/GPi-trials (PDQ-39 SI 4-9 points, ~ 10-26%) except for the fact that no other trials had a significant change in QoL in the BMT group. This resulted in a preference for surgical treatment over medical treatment regarding improvement in QoL in the STN/GPi-trials. One explanation for this difference could be that most patients referred to our clinic for advanced treatment come from smaller hospital in other regions. These referring clinics mainly have outpatient care by general neurologists and geriatricians, and mostly without nurses dedicated to care of neurological disorders. In our experience, most patients have a lot of questions regarding the disease, prognosis, and specific symptoms. All our patients, including those in study I-II, receive information and self-care advice from a nurse with expert knowledge in PD which could explain an increase in QoL without specific motor-improvement.
Patient selection

One important aspect of DBS as a treatment for PD is patient selection. In study I-III, two different selection criteria were used. In study I-II, we used the same criteria as those used for bilateral STN-DBS, with old age, levodopa-response <30% on total UPDRS-III, brain atrophy, significant psychiatric comorbidity, or neuropsychological deficits as excluding factors. Patients deemed unsuitable for bilateral STN surgery can in selected cases be eligible for unilateral surgery\textsuperscript{222}. Historically, and still practiced today, Vim has been used in such cases in patients with tremor as a dominant symptom\textsuperscript{223}. Study III evaluated the long-term results in such a cohort, including some with a limited response of levodopa.

Studies analysing different predictors of good outcome following DBS have found that worse total UPDRS-III scores, worse PDQ-39 scores, and especially a greater response to a levodopa-challenge (e.g. >50%) before surgery is correlated with a better outcome after surgery\textsuperscript{195,307,345}.

Using total UPDRS-III score as an indication of disease severity, the baseline scores Off medication in studies I-III were between 33-42, which is on the lower end of UPDRS-III scores of most STN/GPi-trials (40.8-54) with earlier studies having slightly higher scores. Our blinded trial-cohort was more in line with a study specifically investigating patients with early motor complications (EARLYSTIM) which reported a mean baseline score of 33-33.2\textsuperscript{294}. Total UPDRS-III in open-label studies similarly have higher average scores in earlier studies, with weighted mean of 49.35 between 1993-2004 and 42.55 between 2005-2019 for STN-DBS and 42.65 for GPi-DBS\textsuperscript{307}. The trend to operate on patients with lower disease severity is probably due to the increased experience, and thus confidence, of DBS as a treatment for PD in centres worldwide.

The patient selection for PSA-DBS for PD in the literature is more varied with range of mean/median total UPDRS-III between 28-68 at baseline, or 15.7 regarding contralateral total UPDRS-III\textsuperscript{210}. In the study on 5 bilateral PSA-DBS for PD, Velasco et al. chose patients with 50% of time with poor motor control (“off state”) and H&Y stage 5, indicating severe PD\textsuperscript{208}. 
**Predominant symptoms**

The patients in our cohort had a comparatively higher tremor score in relation to rigidity and bradykinesia. In addition, although we only used UPDRS-IV to measure motor complications, the patients in general reported lower scores than patients in STN/GPi-trials. The inclusion criteria in other studies varied, with some specifying tremor as a minor feature of the patients while others reporting tremor as one of the major features when considering DBS. Indeed, the patients in our cohort had a mean/median tremor-score in the higher span of the reports from both STN/GPi- and PSA-DBS studies.

Regarding PSA-DBS, Velasco et al. report selecting patients mainly with pronounced unilateral tremor and rigidity with mild-moderate bradykinesia, only specifically mentioning dyskinesia and fluctuations in 9/19 patients. In contrast, Plaha et al. reported that 15 out of 35 patients had no tremor at all, while Kitagawa et al. excluded patients without dyskinesia and fluctuations.

Historically, there have been many attempts of subtyping PD to elucidate specific differences in disease progression and response to therapy. Different methods have been used without reaching a consensus on the most useful classification with some having the viewpoint that the subtypes might instead reflect disease stages. The most used subtypes are tremor-dominant PD, postural instability and gait difficulty (PIGD)/akineti-rigid and an intermediate/mixed subtype. In the Veterans administration multicentre study on GPI- and STN-DBS, PIGD-subtype patients had a lower overall motor improvement of UPDRS-III compared with tremor-dominant and intermediate subtypes. Regardless, the results from our studies, together with results from other groups, support the notion that PSA-DBS has a substantial effect on PD tremor regardless of preoperative severity.

To summarise, although the patients in our studies had less fluctuations and more tremor than other DBS trials for PD, DBS targeting the cZi improves Parkinsonism and QoL with a great effect on PD tremor and modest on bradykinesia. In our studies, cZi-DBS did not achieve the same improvement as is seen in the literature on bilateral STN-DBS.
DBS targeting the cZi for Essential tremor

Effects on tremor

In our ET-cohort, we found that unilateral DBS targeting the cZi reduced overall tremor by 61% one year after surgery in comparison to baseline with a similar improvement between On/Off stimulation. Arm tremor was abolished in 78 out of 102 arms contralateral to stimulation. This corresponds to a mean improvement of 94.7%, with only one arm scoring >1 on action tremor at one-year follow-up.

Most published case-series on the effects of DBS primarily targeting PSA for ET come from studies based on our targeting method\(^\text{175,207,212-215,246,354-362}\). As study V analysed the results of all patients operated with cZi-DBS for ET up until 2017 (when we transferred to constant current-devices), there will be considerable overlap to the results of previous studies from our centre. Our results are in line with case series from other groups, showing a range in mean improvement of overall tremor between 64.2-81% from unilateral and bilateral PSA-DBS\(^\text{211,218,219,363-365}\).

In 2019, Dallapiazza et al. published a systematic review on stereotactic surgery for ET, compiling the outcome of DBS and three different lesional procedures; MR-guided focused ultrasound, gamma-knife radiosurgery, and radiofrequency lesioning. In 40 case series of 913 patients with Vim-DBS, they found that the mean overall tremor-reduction by unilateral Vim-DBS ranged between 53.4-62.8%. Specifically, action tremor of the contralateral arm (often the dominant) was improved by unilateral DBS with a wide range between 38.2-78.9%\(^\text{362}\).

Recently, two randomised, double-blinded crossover trials compared the effects of stimulation between contacts located above the intercommissural line (ICL) in the VL thalamus, Vim, and below the ICL, PSA.

In 2018, Barbe et al. reported the one-year results of 13 patients with ET implanted with DBS-electrodes using MER and macrostimulation with Vim as a primary target and "only trajectories through both the Vim and PSA were accepted”. PSA stimulation improved baseline tremor scores by 64% while Vim stimulation improved tremor by 50%. Both contacts significantly improved the patients’ disease related QoL. There was no statistical evidence for carryover-effect between crossover-periods. Adjusted mean
improvement showed slightly, not statistically significant, better tremor reduction by PSA stimulation than Vim stimulation. The patients' own rating of speech was less impacted by PSA stimulation. One of the distinct differences between the groups was a lower current needed to achieve tremor suppression with PSA-contacts than Vim-contacts without changes in pulse width. After unblinding, at one year, 9 of 14 patients had active contacts only in PSA and 3 patients only in Vim.

In 2022, Kvernmo et al. similarly investigated intraindividual differences in stimulation effect between contacts on the same electrode in a mixed diagnosis cohort all with action tremor of the arm. 16 out of 45 patients had ET according to the MDS 2018 tremor classification. They found that PSA stimulation had a greater effect on contralateral arm tremor and hand function than Vim stimulation. At one-year follow-up one of the two contacts below AC-PC-line were used in 91% of patients. Finally, using fixed pulse width and frequency, PSA stimulation used less current than Vim stimulation.

**Effects on motor function**

In study V, unilateral cZi-DBS improved the compound score of contralateral hand tremor and function 83% and ADL by a median of 85% at one-year after surgery in comparison to baseline (-15 and -10 points).

Reports on ADL-scores after unilateral Vim-DBS show a range of mean improvement between 57.9-82% one year after surgery and between 32.3-51% in 5-year follow-up studies. Notably, with a reference to a study by the same authors as the systematic review of DBS for ET, they suggest that there is little difference in disability or QoL between unilateral and bilateral Vim-DBS.

In the PSA- vs Vim-DBS trial by Barbe et al. they reported that PSA-contacts improved a compound score (arm tremor and function) by 68% and Vim-contacts by 54%. The difference between targets did not reach statistical significance. In the trial by Kvernmo et al. they found a mean point reduction of 14.9 by Vim stimulation and 17.55 by PSA stimulation on the compound score with a significant difference between the stimulation location. They had a higher median score at baseline than our cohort (21.8 vs 18) which could be due to the mixed patient cohort with other symptoms than tremor possibly contributing to the hand function. ADL.
scores was considered a secondary endpoint in their study and was reportedly significantly improved but details are to be presented in a separate, yet unpublished, paper.

As such, the results from our studies of cZi-DBS for ET, together with the results of other studies, indicate that PSA-DBS has a reliable and possibly more pronounced effect on tremor, hand function and ADL than Vim-DBS.

**Long-term effects**

Regarding the long-term effects of DBS for ET, although the literature is heterogenous, it is commonly known that the effect deteriorates over time\textsuperscript{366,367}. In study IV, stimulation had a significant effect at each time-point, both compared with baseline and to Off stimulation at the same follow-up. However, some deterioration in effect was seen over time, with mean total ETRS being improved by 66% at one-year and 51% at 10-year follow-up with stimulation in comparison to baseline respectively. A similar difference was seen comparing On vs Off stimulation (63% and 52% respectively). Regarding sub scores, the mean effect on contralateral hand function was reduced by about 2 points at 10-year follow-up compared with one-year.

Regarding long-term effects of PSA-DBS specifically, the only other available results are from another study of our own cohort and a report by Plaha et al.\textsuperscript{357,365}. Plaha et al. found that bilateral cZi-DBS improved total ETRS by 72.6% at follow-up ≥4 years after surgery, which is the same as bilateral stimulation at 10 years in study IV.

Concerning Vim-DBS, a few studies report the effects beyond five years after surgery. Tsuboi et al. reported in about 20 patients followed for ≥6 years an improvement of 68% after one year, and 50% after ≥6 years, when compared to the baseline (n. 97 patients)\textsuperscript{368}. Cury et al. reported ≥10-year outcome in an unknown number of patients out of 38 with uni- or bilateral Vim-DBS\textsuperscript{369}. In this group, stimulation improved total tremor score by 66% at one-year follow-up and 48% at ≥10-year follow-up in comparison to Off stimulation at respective time point. Sydow et al.\textsuperscript{228} reported 19 patients followed for a mean of 6.5 years. Contralateral arm tremor was reduced by 76.6% at one-year and by 59.4% at six-year follow-up compared to baseline. Hand function (both treated and non-treated side) was improved by 45.4% at one-year and 36.9% at 6-year follow-up.
Baizabal-Carvallo et al.\textsuperscript{370} reported a total tremor improvement of 39% on versus Off stimulation in 13 patients evaluated ≥10 years after surgery. Our previous experience of Vim-DBS for ET found that contralateral arm tremor was reduced by 82.4% at one year and 60.3% at last follow-up at a mean of 7 years after surgery, compared with baseline\textsuperscript{371}.

As such, study IV indicates that even though there was a slight deterioration of the effect of cZi-DBS on ET over time, it was not larger than what was found in the literature of Vim-DBS. Looking specifically at the long-term effects on contralateral arm tremor, cZi-DBS seemed to have a more pronounced and reliable effect than what has been reported in long-term studies of Vim-DBS.

The cause and categorisation of this deterioration in effect of both PSA- and Vim-DBS on tremor has been debated. Earlier studies on Vim-DBS introduced the concept of tolerance to describe the waning benefit on tremor\textsuperscript{197,198}. Recently, A. Fasano and R. Helmich proposed more concise definitions where habituation is defined as the loss of previously sustained tremor control, which can occur within days to weeks after DBS programming\textsuperscript{366}. This definition was expanded in a recent review by J. Peters and S. Tisch to include delayed, progressive loss of therapeutic benefit for tremor\textsuperscript{367}. The method of "delta-effect" (comparing Off vs On stimulation, allowing for rebound tremor to settle) at different time-points is currently the most appropriate measure of habituation as this is thought to take disease progression into account.

In study IV, there was no significant change in ETRS-scores Off stimulation over time. Regarding arm tremor and function in patients with unilateral DBS, it was unchanged on the ipsilateral side while the contralateral scores side deteriorated over time. This, together with that the delta-effect seemingly decreased over time, suggest habituation as a likely cause in decrease in efficacy. However, it is recognised that the nature of habituation is not always clear, which can also be said about the perceived relation between this and another stimulation-associated phenomenon, ataxia\textsuperscript{367}. While the decrease in efficacy over time was rather modest, six patients in our long-term cohort, in addition to some in study V, developed what was considered habituation and/or stimulation-induced ataxia of the treated arm leading to a distinctly diminished effect of the treatment. In these patients, multiple sessions of reprogramming, restrictive use of
stimulation and longer periods Off stimulation (stimulation vacation) were implemented with varying degrees of success\textsuperscript{366}. Interestingly, ataxia was mainly seen in the arm and not the lower extremities as otherwise reported\textsuperscript{372}. Whether this is due to unilateral stimulation, having all patients turning the DBS off at night or differences in stimulation location is uncertain.

The notion of ataxia being associated with habituation is supported by a recent study showing that the presence of objectively measured ataxia preoperatively was associated with early habituation/tolerance after Vim-DBS. Although some retrospective studies have found similar improvement of Vim-/PSA-DBS between patients with ‘pure ET’ and ‘ET-plus’\textsuperscript{373-375}, it remains to be seen whether this holds true in prospective cohorts separating patients with/without ataxia specifically. It would be important, and interesting, to see whether patients with ‘ET-plus’ have a higher risk to develop habituation and/or ataxia, especially over time.

\textbf{Awake or Asleep?}

In study V, there was a mostly similar improvement regarding total ETRS (61\%), contralateral arm tremor and function (83\%) and ADL (82\%) between the groups. In addition, they had a similar degree of adverse events, side effects and poor responders. Notably, the awake group had electrodes being implanted (and contacts activated) significantly deeper. This can be explained by the evolution of the surgical technique. When performing awake surgery, after macrostimulation, the electrode was often implanted at such a depth to ensure one contact being located below the intraoperatively established target. With the experience that the most distal contacts were seldom used, when transitioning to asleep surgery, the most distal contact was placed at the target location.

Another difference between the groups was the fact that the asleep group had significantly lower amplitude and PEV than the awake group. This could mean that stimulating more superiorly is a more efficient (under the assumption of equal efficacy). This effect could also be due to lower tremor burden in the asleep group (as indicated by higher arm tremor score in the awake group) or a change in stimulation regime. With the increased experience of patients with early habituation and/or ataxia came the clinical viewpoint of not wanting to risk ‘driving’ this development with
stimulation. This would result in lower stimulation parameters. Since it is difficult to determine the true reason behind the difference in stimulation parameters between the groups, owing to the study being a post-hoc analysis on consecutively operated patients, it is wise to interpret these results with caution.

As previously written, awake surgery has long been the standard approach for DBS surgery. In recent years there has been an increased interest and trend towards asleep surgery with several open-label and two randomized trials comparing asleep and awake DBS with similar results between type of anaesthesia, at least in terms of motor outcome. However, almost all studies have been conducted on patients with PD or dystonia using the STN or GPi as targets.

To our knowledge, only one other group has specifically compared asleep and awake DBS for ET. Two separate studies from the same group at Barrow Neurological Centre in Arizona, USA, have reported the outcome of Vim-DBS. They have analysed data on 56 patients, of which 16 underwent awake and 40 underwent asleep surgery. While they report similar results between cohorts, they used self-reported questionnaires in addition to telephone survey as outcome of effects. In addition, the type of anaesthesia was chosen based on the referring neurologist agreement and patient’s preference which introduces a selection bias. In the first retrospective study, they sent out the questionnaires at a mean of 17.7 months after surgery asking the patients how they would assess both their pre- and postoperative tremor which introduces a significant recollection bias. In the second study, they also measured tremor using a smartphone-based accelerometer, but 12 patients were missing questionnaire data, and 25 sides were missing tremor data at the three-month follow-up. The short follow-up period of their second study could obscure a difference in efficacy between awake and asleep surgery since the tremor-reducing effect of peri-electrode oedema can last for several months in some patients. In the Vim vs PSA-DBS trial by Kvernmo et al., the authors speculate that this oedema-related effect obscured a possible difference between the targets during the first three-month period. In addition, this concept was actively designed and accounted for in the other Vim- vs PSA-DBS trial by Barbe et al.
In our cohort (study V), the results of macrostimulation in four patients in the awake group led to a repositioning of the electrode or implantation of an additional electrode within the PSA in the same session. No patients in the asleep group had an intraoperative relocation of the electrode. Reducing the number of passes in the brain is an important aspect, as multi-track MER and non-image guided surgery have been associated with a higher risk of intracerebral haemorrhage. In addition, a recent meta-analysis of 145 articles with over 7000 patients with reports of complications found that awake surgery had a higher incidence of intracerebral haemorrhage and infection than asleep surgery.

As the results from one of the trials of awake versus asleep DBS for PD suggested, asleep surgery is probably more convenient and less stressful for both the patient and the surgeon; A better quality of MRI images can be achieved since movement artifacts are abolished, possibly resulting in better targeting. A completely horizontal position is uncomfortable for the patient during awake surgery but is not an issue with the patient asleep. Asleep surgery and a horizontal position might reduce the risk of venous air embolism and also increase accuracy; In our subjective experience, shifting from a semi sitting to a horizontal position has reduced CSF-leakage, possibly since the brain will press against the burr hole, thus sealing it. Also, an “asleep” brain with controlled anaesthesia is more haemodynamically stable, and this, combined with an entry point over a gyrus, a very short dura opening time, may minimise CSF-leakage and the occurrence of pneumocephalus.

As indicated by the reduced skin-to-skin time in study V, several parts of the procedure are in our experience faster with the patient asleep. Most importantly, an asleep patient allows the implantation of extension cable and IPG to be done directly (without removing the frame). There is further an economical aspect with awake surgery is more expensive than asleep, especially when MER is used.

There are of course also drawbacks to asleep surgery: It does not allow for intraoperative evaluation of stimulation effects and side effects. This has not been considered as an issue in GPi-DBS, where asleep DBS is common. Further, several groups are today performing STN-DBS asleep. Common for these two targets is that they are easily identified on conventional MRI, enabling visual anatomical targeting and
image-based electrode location verification. This is also the reason why asleep Vim-DBS surgery for ET has been met with more apprehension. As previously written, the Vim cannot be visualized using conventional MRI, and hence atlas coordinates or some equations are used, despite the known interindividual anatomical variation. This is why intraoperative stimulation/MER\textsuperscript{404} are of more importance in Vim surgery. Recently, attempts have been made to overcome this by visualization of the cerebellothalamic fibres passing through the PSA into the Vim\textsuperscript{405,406}, but this technique is still in its infancy and presents issues related to accuracy of merging images\textsuperscript{407}.

In our studies, there was often a pronounced microlesional effect with disappearance of tremor at the introduction of the electrode. Sometimes the depth of the electrode, and rarely other coordinates, were adjusted following macro stimulation. The interpretation of macrostimulation response was sometimes difficult due to the disappearance of tremor due to this ‘stun effect’. However, stimulation was carried out to elicit side effects such as dysarthria, ataxia, and paraesthesia. The interpretation of these side effects can sometimes be bewildering, as we have previously described\textsuperscript{175,408}, and most of them showed adaptation after few seconds or minutes of intraoperative stimulation.

As such, the results of study V indicate that asleep cZi-DBS surgery has similar efficacy as awake surgery, with additional possible benefits of asleep surgery found in the literature. cZi-DBS has a major advantage over Vim-DBS regarding asleep surgery as it allows for visual anatomical targeting and image-based electrode location verification, which may reduce the number of passes in the brain with a subsequent lower risk of intracerebral haemorrhage.

**Adverse events**

**Complications**

In studies I-III there was one major surgical complication (electrode extirpation due to suspected infection) and one deep vein thrombosis three months after surgery. In studies IV-V there were three major surgical complications (one postoperative stroke, one with minor pulmonary embolism, and one inflammatory reaction around the electrode). In all five
studies, with a total of 152 electrode implantations in 117 patients, there were no intracranial haemorrhages. These results compare favourably to the reported prevalence of surgical complications. A systematic review and meta-analysis published in 2023, including over 21,000 patients treated with DBS, found a prevalence of intracranial haemorrhage of 2.4%. In addition, the risk of haemorrhage has been found in two separate reviews to be significantly higher in non-image guided and multi-track MER-studies. In addition, infection rates and hardware complications have been reported to be 4.2% and 2.4% respectively in DBS for PD, with corresponding rates of 1.7%-5.4% and 1.4-3.8% in DBS for ET.

**Stimulation-induced side effects**

Regarding stimulation-induced side effects of cZi-DBS for ET (study V), 9% of our ET-cohort experienced ataxia, 6% early habituation, 5% dysarthria, 2% gait disturbances and 1% experienced paraesthesia by stimulation at one-year follow-up. 4 additional patients experienced mild speech and gait disturbance one year after surgery which were unchanged by stimulation settings. In the literature, studies on unilateral Vim-DBS for ET have reported rates of dysarthria in 11%-38.5%, dysphasia in 9.9%, and ataxia in 9.1-16.7% of patients.

Stimulation-induced side-effects in our patients with PD were harder to evaluate since some symptoms such as gait- and speech disturbances were also present as symptoms of PD. Indeed, a dystonic foot was improved On stimulation while a slight drag of a foot contralateral to stimulation was seen in four patients. In addition, some patients had improved speech On stimulation while others had dysarthria. Notably, of the two patients with stimulation-induced dysarthria in study II, none of the patients had noticed it themselves. In cases where the side effects were disabling, stimulation parameters were adjusted, and the side effects improved without decreased efficacy in most patients. Interestingly, none of our patients with PSA-DBS for PD had stimulation-induced ataxia.

STN-DBS has consistently been found to affect verbal fluency while stimulation-induced dysarthria and hypophonia have been reported in 4-17% of patients. Other side-effects include eyelid opening apraxia, motor contraction and many more, although those inducing permanent impairment are relatively rare.
Regarding cognitive and mood related outcomes, we have previously found that cZi-DBS produces a slight decrease in verbal fluency similar to Vim- and STN-DBS\textsuperscript{361}. Regarding the effects on mood, patients with PD reported decreased anxiety after cZi-DBS surgery. In addition, self-reported apathy did not increase\textsuperscript{341}. In study II, one patient with PD developed dopamine dysregulation syndrome after the 6-month evaluation with a significant increased intake of dopaminergic medication against the advice of the neurologist. In the ET-cohort, one patient developed depression following surgery. This patient had experienced recurrent depression and been medicated for depression several times prior to surgery. Changes in the stimulation parameters did not affect the patient’s mood. As such, in our experience, DBS targeting the cZi had similar stimulation-induced side effects as the literature on Vim-DBS\textsuperscript{362} while we did not see the same side effects on mood as have been reported following STN-DBS for PD\textsuperscript{189-193}.

**What are we stimulating?**

The current hypothesis of the effects of DBS relates to the notion of PD and ET being circuitopathies, meaning that regardless of origin of a pathological process, there is a resulting dysfunctional signalling on a network level\textsuperscript{144,145,152,237}. Accumulated evidence from molecular, cellular, and most importantly from neurophysiological studies on animal models and patients with PD, suggests that DBS restores the signalling pattern in motor circuits to a more physiological state\textsuperscript{410,411}. This seems to be achieved by several possible processes resulting in a decoupling of the cell bodies from afferent and efferent fibres in addition to directly generating action potentials in nearby axons. Although the effects of DBS on non-neural tissue should not be underestimated, I will leave this topic for the sake of the following discussion\textsuperscript{411}.

Together with the fact that axons, especially if large and myelinated, have a higher level of excitability than cell bodies, one could argue that a substantial part of the effects of DBS is achieved by affecting fibres\textsuperscript{410}. 
**What is the target?**

In my opinion, the most important aspect when speculating on the relation of the effects of DBS to structural and functional anatomy is to separate "target"-DBS and the actual anatomical structures ultimately affected by the stimulation. As previously written, analysing contact location of what is being called “Vim-DBS” and “STN-DBS”, revealed the primary stimulation site to be located outside of the targeted structures to a significant degree\(^{216,218-220,412}\). The same could be said about the studies in this thesis. Regardless of localisation methodology, all studies in this thesis consistently found that despite targeting the \(cZi\) at the level of the equator of RN, the average location of the contacts used for stimulation are mostly concentrated superior to the “target”, about halfway to the VL thalamus. Indeed, this was the case for both patients with ET and patients with PD. Moreover, some patients were found to have active contacts at the “target level of \(cZi\)”, while others had active contacts in the VL thalamus.

The discrepancy between the target used for DBS and location of stimulation should be viewed in the light of what is the main determinant of choice of contact: the clinical response. Apart from studies like the intraindividual cross-over trials of Vim- vs PSA-DBS, the response during monopolar review and subsequent programming sessions determines which contacts to be used. While one could argue that stimulation of \(cZi\) proper has not been adequately investigated in the studies of this thesis, there is a reason why the programming led to stimulating further away. Indeed, this would instead support the notion that \(cZi\) is not a superior target to the STN, as boldly claimed in other studies\(^{210}\). While the clinician performing the programming can partly be selective in which symptom they want to try to alleviate, the settings used in our PD-studies was optimised to achieve effects on tremor as well as bradykinesia and rigidity.

However, despite efforts to elucidate differences in stimulation location between good/poor responders after optimised programming, this could not be achieved in the studies of this thesis.

**What is the issue?**

To use a quote ingrained in most medical students during their histopathological education; *tissue is the issue*. This was known during the lesional era when the teams performing stereotactic lesional surgery.
Discussion/What are we stimulating?

consisted not only of dedicated clinicians but also included anatomists as a crucial part of the team. By combining the clinical and neurophysiological results with postmortem investigations, they were able to identify and verify key structures involved in the pathophysiology of tremor, such as the VL thalamus. In addition, by following the results of Wallerian degeneration, they could relate the clinical effects to specific fibre pathways. With the invention of DBS and especially MRI, the anatomoclinical studies fell out of favour. Indeed, postmortem studies of DBS have only been done in a handful of cases\textsuperscript{413}.

As we are implanting and evaluating electrodes in vivo, all localisation methods are indirect estimations. Every step of the process has its own limitations and inherent variability some of which are mentioned below:

- **Methodological**: Intraoperative stereotactic coordinates with biosignatures from neurophysiological testing vs electrode artefact localisation on imaging. Contact location vs VNA. Acute effects of stimulation vs chronic stimulation effects.

- **Technological**: Imaging modality and sequences used, affecting the size and shape of anatomy and electrode artifact (MRI, CT, fluoroscopy, plain film X-ray, deterministic vs probabilistic tractography etc.). Merge-errors between pre-and postoperative imaging (and tractography). Electrode localisation algorithm errors. VNA-calculations.

- **Interpretation**: Interobserver differences in assignment of AC & PC, estimation of contact location based on image artifact, choice of reporting method, nomenclature etc.

- **Group-analysis**: Interindividual variation of anatomy, normalisation algorithm errors, patient-to-group domain merge errors etc.

As aptly put by the idiom – *many small streams make one mighty river* – several millimetre/submillimetre errors can add up and lead to a significant difference between estimated and actual electrode location in the individual patient and especially in group-level analyses.

This issue probably plays an important role why there have been such a discrepancy in localising a sweet spot for stereotactic surgery. The STN has been used as a target for DBS for 30 years and is by far the most extensively studied target. In a recent systematic review by de Roquemaurel et al. over
half of studies suggested the superolateral of the STN as the “sweet spot” for STN-DBS, while the remaining studies were either inconclusive or suggested better outcome in adjacent white matter, including medial to the STN. This review highlighted another issue, namely that out of 439 possible references only 24 were deemed to have reported enough data for cross-studies comparisons.

The studies in this thesis have utilised different methods to estimate and report stimulation location: MRI-CT images at the level of the active contacts with corresponding MCP- and pSTN-coordinates (study I), VNA-based improvement maps in a patient-cohort based anatomical space (study II), overlapping binary VNAs into an histological-MRI-atlas based space through reversed atlas-to-patient transforms with a comparison to commonly used stereotactic atlases (study III), only MCP-coordinates (study IV) and plotting mean active contacts ± SD in relation to pSTN on a stereotactic atlas (study V). Together with previous studies with VNA-models of both monopolar review data and clinical stimulation parameters of the ET-cohort, all studies consistently showed a common area directly below the VL thalamus through which cZi-DBS achieved its effect.

Regarding previous studies on PSA-DBS, the locations of the active contact have been reported in different ways, if at all, and the same can be said about stimulation parameters. Previous reports of PSA-DBS for PD have used the active contact location method. Besides confirming that the contacts are in the PSA, as opposed to the STN, attempts to narrow the optimal site within the PSA has not been fruitful. Castro et al. found no significant difference in MCP-coordinates between optimal and suboptimal outcome following DBS targeting Raprl. This could be due to the limitations of using MCP-coordinates to estimate contact location. The interindividual differences in anatomy, both regarding fibre tracts and nuclei such as the STN, can be significant. Studies on the distance of the borders of the STN defined on MRI and comparisons of the fibre tracts using histopathology have found interindividual differences up to several millimetres. To account for this variation in anatomy, we have used a reference point closer to the electrode, such as the pSTN, rather than the MCP to estimate the contact location. While we have yet to perform a comparison study between these methods, our impression is that using pSTN as a reference point might better reflect what we see on CT-MR images.
Velasco et al. have recently investigated interindividual variations of fibre tracts in the PSA using tractography. They did not find significant intra- or interindividual differences in stereotactic coordinates of three differently seeded tracts in 10 PD patients and 10 healthy controls. However, they did find a significant variation in the stereotactic position of the point where the most significant number of ‘fibres’ is concentrated in the smallest volume.

Another limitation on subdividing the PSA according to outcome relates to its topography and size. The area where one can place an electrode and call it PSA-DBS is restricted to an area of a few mm in diameter. Hence, even if different groups might differ in their preferred target within the PSA, there will be a considerable overlap in the final location of contacts used for stimulation, and an even larger overlap in the volume of tissue affected by the stimulation. This has recently been demonstrated in a large multicentre study using PSMs to evaluate the optimal site of stimulation for tremor.

In this paper, the results of Vim/PSA-DBS in 119 patients from five European centres was used to create individual VNAs directly in an MNI space using an open-source software called Lead-DBS. By combining the VNAs and their clinical outcome, they computed PSMs for each hemisphere into the MNI space. This resulted in PSMs based on 237 hemispheres with corresponding tremor reduction data. They managed to find a significant cluster corresponding to good tremor response located just beneath the Vim and partly overlapping the CTT. This supports the notion of the PSA being a more efficient/effective target and that the CTT is most likely the main anatomical target for stimulation. However, the images in the paper also show a huge variation in the stimulation locations among excellent responders with a significant overlap with the location of poor responders. In addition, predictive models of the map, while statistically significant, only explained 14% of the variance in tremor improvement. These two results support the notion of seeing the DBS target for tremor as a continuum (see next section), rather than a specific point, and that the current VNA and anatomy models (tractography, atlases) are probably limited in their specificity.

Another aspect is related to the commonly used DBS-targets as being parts of the same motor circuitry. If there is a disturbance in one part of this circuitry, the resulting dysfunctional signalling travels to and affects in other parts of the same circuitry. It stands to reason that it is possible to
achieve similar effects, such as restoring function, by targeting different parts of the same circuit, nuclei as well as fibre pathways. This has indeed been the reasoning of stereotactic neurosurgeons for decades and has in modern times been translated into the notion of “Connectomic Deep Brain Stimulation”\textsuperscript{416}.

**What is my angle?**

Based on the results of clinical and anatomical studies of DBS together with the notion of circuitopathy, it would perhaps be better to see DBS-targets as existing on a continuum in which there is a region, not a spot, upon where electrical stimulation causes symptomatic relief. The borders of this continuum, and shape and size of the region will differ according to which symptom DBS is sought to alleviate and its corresponding pathophysiological basis. This is reflected in the notion that there is a slight room for error in every target in which the outcome will be good.

This continuum becomes evident when looking at the different DBS-targets for tremor. Vim/VLp nucleus of the thalamus lies most superiorly and has a varying spread in the mediolateral and anteroposterior direction. Below lie fibre bundles in part in a seemingly somatotopic fashion but in a criss-crossing and winding pattern. These fibres have both short-and far-reaching connections of which the two most important for movement disorder-DBS seem to be the pallidothalamic fibres (PTT/al, fl, tl/H1,H2) and cerebellothalamic fibres (CTT/fct/DRTT/Raprl). These fibre bundles are interspersed in the subthalamic area in between the RN, STN and Zi. To unify the findings that the most optimal contacts of Vim-DBS sometimes lie at the border of/inferior to the thalamus with the results of cZi/Raprl-DBS, the name *PSA*-DBS would arguably better reflect the region where stimulation reliably alleviates tremor to a high degree.

However, as these structures all lie within a tree-dimensional space, it is possible to target each individual structure from different angles. Depending on the target and the trajectory, the same electrode can traverse through several structures, as has been done in comparative studies of Vim vs PSA-DBS\textsuperscript{392,393,417-419}. By the same principle, using an identical target but different trajectories will traverse other anatomical structures. When finally applying electrical stimulation, different stimulation parameters will
determine both the reach of the stimulation and the degree of neurons/axons activated within the stimulated area.

Looking at the axial slices of MRI-images and coordinates of Velasco et al. revealed that their target is slightly more medial and anterior to ours. However, they specifically used a smaller mediolateral angle (<10 degrees) to ensure a trajectory “parallel to the midline”. By placing the burr hole at the level of the coronal suture, the trajectory in relation to the target would be in an anterior-leaning angle. Depending on the degree of the angle, this would result in the two most distal contacts being located close to CTT while the two most proximal contacts to be located close to PTT. Their stimulation parameter regime involved activating two adjacent pairs of contacts. In their earlier reports they used the two most distal contacts but with an average pulse width of 232µs together with 2.8V, probably resulting in a significant spreading of the current. In later reports, they used a pulse width of 90µs but instead the two middle contacts. Speculatively, this suggests that they more reliably stimulate the PTT in addition to the CTT. The prominent effect of PTT-stimulation on rigidity would be in line with the standard model of the pathophysiology of Parkinsonism as well as results from lesional surgery of the PTT using radiofrequency or MR-guided focused ultrasound\(^15\),\(^420\)-\(^422\). Indeed, this was known during the lesional era where ablation of the CTT/cerebellar-receiving nucleus of the thalamus resulted in a good effect on tremor while bradykinesia and rigidity were only partly relieved. This necessitated further lesions of the PTT/pallidal-receiving nucleus of the thalamus for effective control of these symptoms\(^423\).

When looking at the location of contacts and the targeting method by Kitagawa et al. they report both a more anterior location in addition to two contacts in and superior to the STN. Both locations would correspond to a close location to pallidothalamic fibres as well as STN-neurons.

Finally, Plaha et al. analysed three slightly different similar targeting methods\(^210\). Based on the angles demonstrated and the plotted location on the atlas according to MCP-coordinates, the active contacts used for cZi-DBS were located more anterior, lateral, and closer to the STN than the contacts in our studies. As such, stimulation through the cZi-contacts would in their study theoretically spread to a larger degree to the STN than what we achieved.
In Figure 21, a side-by-side comparison of the hypothetical differences in trajectory between our method and the other PSA-DBS studies are shown. The electrodes were transposed into the Yelnik-Bardinet atlas using Suretune™ based on mean position, images and angles/approach described in the respective studies. As is shown, speculatively, Velasco et al. end up closer to the PTT while Plaha et al. closer to the STN.

As such, the angles used during targeting could be one possible explanation for the differences in effect on Parkinsonism between our studies and other PSA-DBS studies. With Velasco et al. more reliably coming closer to PTT...
leading to better results on rigidity, and Plaha et al. being closer to the STN, leading to better results on bradykinesia as well.

Additionally, Plaha et al. changed their targeting procedure when they noticed a better outcome among patients with STN-DBS whose active contact was near the pallidofugal-fibres and rZi, dorsomedial/medial to the STN.

Indeed, side effects are known to limit the potential effects of different targets, including Vim-, STN- and PSA-DBS. As such, the optimal DBS target should be in an area tolerant to side effects while at the same time allowing for modulation of dysfunctional pathways.

As previously written, the results of our studies showed a trend towards stimulation coverage overlapping both the CTT and Zi. However, if Zi has the same function in humans as rodents, and we were to activate all neurons/axons close to the electrode, we should see a lot more, and more disturbing, side effects than what we did. This could either mean that Zi is less susceptible to modulation by the therapeutic stimulation regime or due to factors such as different function of the Zi in humans, limitations in patient-specific transform to common space, usage of histological atlases or limitations in the electric field simulations.

Utilising electric field thresholds to define the VNA has been widely used, probably due to its simple processing requirements and the fact that this seems to agree with when the first clinical response is seen, as indicated by clinical response studies. However, the assumption of an equal activation of the neural tissue within the simulated volume is a potential issue. As the electric field strength is not homogeneous throughout the volume (with diminishing strength farther away from the electrode), the degree of axons activated should arguably not be homogeneous either. The closer to the electrode, the more axons should be activated. This concept is shown in Figure 22, from a paper by J. Johansson in 2021, revealing the estimated fraction of axons activated (%) by stimulation around different types of electrodes. Thus, visualisation of a field simulation using a specific isolevel reveals the border where axons are beginning to be activated by the electrical stimulation. However, the visualised simulation does not correspond to an activation of all neurons within the visualised border/volume.
A similar issue is seen when using binary VNAs when creating PSMs, as the voxels are only classified into "being activated" or "not activated" instead of generating a gradient of activation.

![Electric field simulations and estimations of fraction of activated axons surrounding different types of electrodes with the 0-border representing an EF isolevel of 0.19 V/mm in (a) and 0.15 V/mm in (b) and (c).](image)

*Figure 22. Electric field simulations and estimations of fraction of activated axons surrounding different types of electrodes with the 0-border representing an EF isolevel of 0.19 V/mm in (a) and 0.15 V/mm in (b) and (c). Taken unedited from J. Johansson, 2021.*

One way to account for this concept is using a weighting function. This can be derived either from the electric field or from distance to the electrode, as first introduced by Eisenstein et al.\textsuperscript{249} The difference between PSMs based on weighting function and PSMs from binary VNAs has been analysed in a study by T. Nordin et al.\textsuperscript{255} evaluating methodological aspects of the creation of PSMs. They found that weighting function has an impact mainly on the statistical significance but is of less importance in visual analysis of mean improvement maps.

Other studies creating PSMs have in some cases also performed prediction analysis\textsuperscript{254,427,428}. This was not performed in study II due to the low level of significance in the statistical test, but the result can be seen as a spatial visualization of the improvement in the cohort as was also done in study III. On the other hand, many studies creating PSMs have used “no improvement” as the null hypothesis to test against while we classified patients according to improvement seen in STN/GPi-DBS. The “no improvement” goes against the knowledge that the region where stimulation has some improvement is relatively large\textsuperscript{246,415}. It would perhaps be more appropriate to test against the mean improvement\textsuperscript{255}. 
Another way to elucidate the improvement of different symptoms of PD is by using data from monopolar reviews, which would provide more spatial information and smaller electrical fields. This factor was found to have a higher impact on PSMs in the methodology-study by Nordin et al. The downside however, is that one only sees the acute effects of stimulation and might not fully reflect the contacts used for chronic stimulation. As with levodopa, it is known that there are immediate effects and more slowly developing effects of stimulation. While there are differences between targets and diseases, it is generally viewed that DBS has an immediate effect on tremor and a slower effect on bradykinesia and rigidity. Several studies have found that a waiting period of 60-90 minutes between Off/On stimulation suffices when evaluating the cardinal symptoms of PD, while there have been indications of day-to-week long latencies in certain effects, especially regarding gait and dystonia.

In my opinion, electric field simulation is a necessary development to increase our understanding of DBS and improve the treatment. However, it is important to recognise the limitations of the current models and different methods of correlating the simulations to clinical outcome. Limiting factors such as that activation of axons depend on where along the axon the stimulation occurs, the orientation and diameter of the axon, the necessity for larger sample sizes, and an incomplete understanding in the mechanism of DBS to name a few.

Nevertheless, by inserting an electrode with the tip in the area posteromedial to the STN at the level of substantia nigra with certain anteroposterior and mediolateral angles should lead to a higher chance of having at least one contact in an optimal location. In the case of targeting cZi for tremor, this would mean that one can reliably achieve tremor relief with as little stimulation strength as possible to minimise the spread of the current resulting in unwanted side effects.

Future studies reporting on the effects of DBS should make an effort to include not only the target itself, but the trajectory and/or the stimulation location as well. Indeed, this process has partly begun by the spread of open-source software such as Lead-DBS, although the current visual presentation in papers often results in cluttered images and should be complemented by an axial view for neurosurgeons to be able to replicate the targeting method.
Discussion/Why does it work?

Why does it work?

**CTT – the common denominator**

While it is not possible to ascertain the mechanism through which we alleviate tremor by cZi/PSA-DBS from the studies of this thesis, I will try to harmonise our findings with current pathophysiological models for tremor generation. While we cannot rule out Zi as an important node, the results discussed so far gravitate towards modulation of the cerebello-thalamo-cortical circuit by affecting the CTT. Considering Vim-, DRTT/CTT-, PSA- or cZi-DBS all as ways of targeting this circuit, the notion of stimulation in the PSA below the VL thalamus as more effective/efficient becomes apparent. Just like the corticospinal tract from the motor cortex down through the internal capsule to the spinal cord, the CTT is shaped like a funnel with its' connections being spread out in the thalamus while being more densely packed inferiorly in the subthalamic area. This notion was known during the lesional era, as emphasized by Bertrand et al. in 1968 (although they argued PTT over CTT), and this ‘funnel’ notion has been a recurring explanation to why PSA/cZi-stimulation would be more effective than Vim-stimulation.

As written in the background, there is compelling evidence from imaging, neurophysiological, lesional and treatment-related studies for a dysfunction in the cerebello-thalamo-cortical circuit as the main part of ET pathophysiology. A recent study reviewed the results of structural and metabolic studies on ET, identifying the cerebellum to be the only brain region to be functionally connected to the findings in over 90% of the studies. In this study, they also found an overlap of the functional connectivity network to the network where lesions have been found to relieve tremor, with the VL thalamus and the cerebellum being key regions.

Regarding PD tremor, the dimmer-switch hypothesis put forth by R. Helmich argues for an involvement of both the cerebello-thalamo-cortical circuit and the BGa with the different subcircuits and/or nodes being associated with different roles in tremor generation. This hypothesis is based on findings of tremor-related oscillations and changes in local field potential in the BG (GPI and STN), imaging studies’ findings of tremor-related changes in the activity in the cerebello-thalamo-cortical circuit and
putamen and the attenuation of different aspects of PD tremor by transcranial cerebellar and cortical stimulation. According to this model, the BG are transiently activated at the onset of tremor, acting like a light switch turning “on” the tremor-activity. The cerebello-thalamo-cortical circuit then maintains and modulates the power of the tremor, acting as a dimmer. While the temporal, etiologic and pathogenetic aspects of this model are not entirely established, follow-up studies by the same group have further strengthened the dual relationship of these circuits with possible differences in involvement by the cerebellum between rest-tremor and re-emergent postural tremor.

DBS targeting the cZi would thus act upon both the on/off-switch (basal ganglia connections) and the dimmer/tremor maintenance by modulation of the CTT regarding PD tremor while acting mostly on the CTT regarding ET.

Limitations

Overall limitations such as small sample sizes and non-blinded evaluations should warrant caution when interpreting the results. On the other hand, the same evaluator rated all patients with PD (Study II-III) at baseline, short-term and long-term follow-up, and comparisons between non-blinded and blinded evaluation are not always different.

Study I: At baseline, the disease duration and total UPDRS-III scores Off medication were seemingly lower in the surgical group than in the medical group but this was not statistically significant. This might be a consequence of the non-stratified randomisation in a small sample size, and it is possible that the differences would have reached significance in a larger sample. However, at the 6-month follow-up, the non-significant differences in off-medication total UPDRS-III scores had clearly decreased with similar standard deviations.

Study II: Although it was possible to create improvement maps and estimate areas for stimulation based on a template of the patient cohorts’ anatomy, neither a statistical sweet spot nor a clear-cut relationship between location of stimulation fields and the degree of symptom relief could be discerned. This might be due to limitation in the clinical data (small sample, cohort heterogeneity etc.), small distribution of electrode
location within the PSA (less variations) and power of the statistical method. In addition, the use of chronic stimulation parameters instead of results from the monopolar review limited the spatial distribution and clinical data points. The cut-off for the responder groups was based on a review of studies on STN-GPi-DBS for PD but this division led to a skewed distribution of the responder-groups.

**Study III:** The sample size increases the risk of type II errors, which could be contributing to, but probably not fully explain, the modest effects on rigidity and bradykinesia compared to previous PSA-DBS. The simulations used in Suretune™ have inherent limitations such as not accounting for differences in conductivity of different biological tissues (e.g., white matter vs grey matter). However, it has been shown that for constant voltage-stimulations, this difference does not affect the VNA to a significant degree. As with study II, the small sample size and lack of monopolar review-data limited the possibility to perform statistical tests of the VNAs in relation to the clinical outcome. Further, the merge, modelling and transform of patient-specific imaging to a common domain comes with the risk of incremental deviation of contact location in relation to the anatomy. To mitigate this, two different people compared the contact location in the 3D domain to each patients’ CT-MRI-fusion.

**Study IV:** There was a considerable drop-out rate in this study. Half of the patients were not available for follow-up after 10 years. This is similar to other long-term studies drop-out rates between 40-66%. In our study, the patients who were deceased prior to 10-year follow-up were older, with a longer disease duration, higher ETRS score and a larger decrease of the stimulation effect over time than the survivors. The higher tremor score before and after surgery was likely a consequence of the higher age, as we have previously demonstrated. However, the larger deterioration of the effect of stimulation seems to be explained by a more pronounced tendency to habituation in this group, for reasons unclear in this material.

**Study V:** The major limitation of this study is that this was not a prospective comparative trial, and thus no randomisation between asleep and awake DBS was done. To conclusively establish differences between awake and asleep surgery for ET, a randomised, blinded trial as has been done regarding PD is necessary. Another possible limitation is that
Discussion/Where does cZi fit into the armamentarium of DBS treatments?

Asleep DBS in our cohort was used after the surgeon had accumulated more than a decade experience of awake DBS, allowing for an in-depth knowledge of the anatomy and macrostimulation physiology of the target area and its surroundings. This may well have facilitated the confidence in implementing asleep DBS, without compromising the good results. The increased experience in cZi-DBS for tremor is possibly reflected in another limitation, namely differences in tremor scores at baseline. The patients that underwent awake surgery had slightly more arm tremor than the asleep group. The successive transition to operate patients with less severe symptoms with increasing experience is also reflected in the literature of DBS for PD, with patients in STN-DBS operated 1993-2005 having longer disease duration and higher UPDRS-II/III-scores at baseline compared with studies published between 2005-2019.

Where does cZi fit into the armamentarium of DBS treatments?

As a treatment for PD

To conclude, although the patient cohort was skewed towards tremor and the location of the stimulation was slightly different from previous PSA-DBS studies, we were unable to replicate a clear benefit of cZi-DBS for Parkinsonism when compared with the literature of STN- and Gpi-DBS. However, the consistent findings that there is a robust, long-term effect of cZi-DBS on PD tremor together with an effect on bradykinesia and rigidity indicates that it is a potential replacement for Vim-DBS. In addition, the close relation of cZi to the STN makes it possible to target and to verify appropriate electrode location using conventional MRI, thus enabling asleep surgery.

As such, for patients with PD ineligible for bilateral surgery with tremor as a dominant symptom, I would argue that unilateral cZi-DBS is preferable over Vim-DBS. Regarding unilateral cZi-DBS vs unilateral STN-DBS, it would be interesting to see a randomised trial in a selected cohort to investigate whether there is a difference in effects on motor symptoms, cognitive and mood related side effects.
As a treatment for ET

There are two randomised blinded trials of PSA-DBS vs Vim-DBS and several open-label trials showing that the PSA is possibly more effective, and definitely more efficient, as a target for ET. The studies of this thesis contribute by providing the first long-term results showing a lasting, albeit slightly diminishing, effect of cZi-DBS for ET. Additionally, we found that the energy consumption was stable over time. Further, the energy consumption of cZi-DBS in the studies of this thesis was lower than what has been reported in the literature of Vim-DBS\(^\text{228,368-371}\). This is especially important as there have been reports of shorter battery longevity of newer non-rechargeable IPGs\(^\text{446}\). In younger patients, this means several IPG-replacements during their lifetime with an incremental increased risk of infection necessitating partial removal of the DBS-system\(^\text{447}\). Further, by using our targeting method, it is possible to place the electrode with high accuracy in a region where stimulation will have an excellent effect on tremor without debilitating side effects for most patients. This targeting method enables asleep surgery, reducing the procedure time, potentially reducing surgical risks, and improving patient comfort.

Regarding replacing Vim with cZi for ET, in the practical sense this comes down to the knowledge, experience and resources of the centre performing the surgery. If a team is experienced and comfortable with Vim-DBS using single-pass MER/macrostimulation and achieves a high degree of good outcome with a low degree of complications, the risks associated with learning a new target might outweigh possible benefits.

For centres with variable outcomes and to neurosurgeons and neurologists starting their stereotactic career, I would suggest targeting the cZi/PSA.

Finally, I believe it to be highly likely that with an increased knowledge about the interindividual differences in subthalamic anatomy, mechanisms of DBS, and the introduction of adaptive DBS\(^\text{448}\), targeting the Vim as is done today will probably not be used in the future. Whether newer methods such as targeting a hypointensity on FGATIR-MRI, CTT using tractography, or using artificial intelligence will be superior to targeting the cZi is difficult to predict\(^\text{449-453}\). There are several technological and methodological issues to overcome such as reducing merge error, reducing the computational time of tractography, limitations of available VNA-models, and size of available electrodes to name a few.
Conclusion

I) Bilateral cZi-DBS alleviates Parkinsonism and seems to improve quality of life. The effect is pronounced regarding tremor and modest regarding bradykinesia. It does not result in the reduction of LEDD.

II) Based on simulations of the electric field and location of the active contacts, the stimulation of cZi-DBS is concentrated within the PSA but VNAs did not reveal any clear differences between good/moderate/poor responders in a small cohort.

III) Unilateral cZi-DBS has an undiminished beneficial effect on PD tremor at a mean of five years after surgery.

IV) cZi-DBS significantly improves ET 10 years after surgery with a slight deterioration in effect over time.

V) Targeting the cZi enables patients with ET to undergo DBS-surgery asleep with seemingly similar benefits as awake surgery at lower stimulation strength and without an increase in procedure-related adverse events.
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