Swallowing function in patients with Parkinson’s disease and Deep Brain Stimulation

Stina Sundstedt
Dedicated to all those who contribute to new knowledge by taking part in medical research.
# Table of Contents

Abstract v
Abbreviations vii
Sammanfattning på svenska x

## Introduction
- Parkinson’s disease 1
- Swallowing function 1
- Assessment of swallowing function 3
- Parkinson’s disease and swallowing problems 4
- Parkinson’s disease and swallow-specific quality of life 4
- Treatment for Parkinson’s disease 5
- Deep Brain Stimulation 5
- Swallowing function and Deep Brain Stimulation 7

## Purpose of the study

## Materials and methods
- Participants 11
  - Paper I – STN DBS 11
  - Paper II and Paper III – cZI DBS 11
  - Paper IV - Swallow-specific Quality of Life 13
- Procedures and data material 14
  - Evaluation of the swallowing function 14
  - VA-scale and QOL-related swallowing questions 15
  - BMI and UPDRS-items 16
  - Swallowing Quality of life 16
- Data and statistical analysis 17

## Results
- Paper I - STN DBS 19
- Paper II - cZI DBS 20
  - Self-assessments 21
- Paper III - cZI DBS 22
- Paper IV- cZI DBS 25
  - PD group vs. Control group 28
- Intra-rater and inter-rater reliability 28

## Discussion
- Effect of DBS on self-estimated swallowing function 31
- Effect of cZI DBS on swallowing related secondary and non-motor features 31
- Effect of cZI DBS on swallow-specific QOL 32
- Swallow-specific QOL in patients with cZI DBS vs. controls 33
- Strengths and limitations of the studies 33
- Future research and clinical implications 34

## Conclusions 36

## Acknowledgements 37
<table>
<thead>
<tr>
<th>Funding</th>
<th>38</th>
</tr>
</thead>
<tbody>
<tr>
<td>References</td>
<td>39</td>
</tr>
</tbody>
</table>
Abstract

Background

Parkinson’s disease (PD) is one of the most common neurodegenerative diseases in Europe. Besides motor dysfunction, PD is characterized by several non-motor and secondary motor features, such as weight change, sialorrhea, constipation and swallowing problems. Of these, swallowing is one of the most critical, as it is associated with aspiration pneumonia and consequently is the comorbidity with the highest mortality rate. Swallowing problems affect four of every five patients with PD, and even mild swallowing problems have notable psychosocial effects for patients and their caregivers. Consequently, it is essential to find treatment strategies for PD that may alleviate symptoms for patients with swallowing problems and their potential consequences.

Deep Brain Stimulation (DBS) is a surgical treatment option for PD, which improves overall motor function and quality of life, but its effect on swallowing function is not clear.

The purpose of this thesis was to contribute to the understanding of the effect of deep brain stimulation in the subthalamic nucleus (STN DBS) and the caudal zona incerta (cZI DBS) on pharyngeal swallowing function and on swallow-specific quality of life in patients with PD.

The specific aims were to assess longitudinally the effect of STN DBS and cZI DBS on swallowing at 6 and 12 months postoperatively, in order to identify possible effects of the DBS on swallowing function. In addition, the effects of cZI DBS on ratings of swallowing-related non-motor and secondary motor features such as body weight changes, sialorrhea and speech problems were to be assessed.

Methods

Eleven PD patients with STN DBS (Paper I) and seventeen patients with cZI DBS (Paper II-IV) were included in this thesis. All patients were evaluated preoperatively and 6 and 12 months postoperatively. The effect of STN DBS and cZI DBS on swallowing was assessed with Fibreoptic-Endoscopic Evaluation of Swallowing (FEES) according to a predefined protocol including Penetration-Aspiration scale, Secretion Severity scale, preswallow spillage, pharyngeal residue, and pharyngeal clearance. Self-assessments were addressed using a visual analogue scale. The cZI DBS patients also
completed the Swallowing Quality of Life (SWAL-QOL) questionnaire. Weight changes measured by Body Mass Index, and specific items from the Unified Parkinson’s Disease Rating Scale were also examined. Nine controls without PD were included in Paper IV, by answering the SWAL-QOL questionnaire.

**Results**

No clear effect of DBS on swallowing function or swallow-specific quality of life could be observed. There was no effect of DBS on the occurrence of aspiration, secretion, pharyngeal residue or clearance in the study groups with STN DBS or cZI DBS. Patients with STN DBS reported a subjective improvement in swallowing function with DBS stimulation turned on at 6 and 12 months after surgery.

In patients with cZI DBS, the median body mass index was postoperatively increased with 1.1kg/m² and the median increase in weight were +3.0 kg after 12 months with cZI DBS.

The scores from the SWAL-QOL questionnaire were high overall in the group with cZI DBS, and the scores were unaffected by the cZI DBS surgery and stimulation. The SWAL-QOL total score was not significantly different between the PD patients and the controls, but the scores from the ‘burden’ and the ‘symptom’ subscales were worse in PD patients.

**Conclusions**

STN DBS or cZI DBS did not have a negative effect on swallowing function or ratings of swallow-specific ‘quality of life’ aspects in this cohort. Patients with STN DBS reported a self-perceived improvement in swallowing function when DBS was turned on. With regard to swallowing, patients with cZI DBS had an overall good quality of life throughout the conduct of the study and their swallow-specific quality of life was not negatively affected by cZI DBS. There seems to be no increased risk for aspiration or penetration due to surgery or stimulation for either the STN DBS or the cZI DBS groups. cZI DBS caused weight gain postoperatively. Since the sample sizes in these cohorts are small, the findings need to be confirmed in larger studies.
Abbreviations

The following abbreviations are used in the text

PD  Parkinson’s Disease
VFSS  Video Fluoroscopic Swallowing Study
FEES  Fibroptic-Endoscopic Evaluation of Swallowing
DHI  Dysphagia Handicap Index
MDADI  M.D. Anderson Dysphagia Inventory
SWAL-QOL  Swallowing Quality of Life
QOL  Quality of Life
LEDD  Levodopa Equivalent Daily Dose
L-Dopa  Levodopa
DBS  Deep Brain Stimulation
STN  Subthalamic Nucleus
STN DBS  Subthalamic Nucleus Deep Brain Stimulation
PSA  Posterior Subthalamic Area
cZI  caudal Zona Incerta
cZI DBS  caudal Zona Incerta Deep Brain Stimulation
GPI  Globus Pallidus internus
CAPSIT-PD  Core Assessment Program for Surgical Interventional Therapies in Parkinson's Disease
UPDRS  Unified Parkinson's Disease Rating Scale
BMI  Body Mass Index
VA-scale  Visual Analogue scale
P/A  Penetration-Aspiration
PS  Preswallow Spillage
Phr  Pharyngeal residue
CC  Pharyngeal clearance
SS  Secretion Severity scale
C₁  Consistency 1: water
| C\textsubscript{2} | Consistency 2: 50 ml water with 5 ml jellification powder |
| C\textsubscript{3} | Consistency 3: 50 ml water with 10 ml jellification powder |
| C\textsubscript{4} | Consistency 4: 50 ml water with 15 ml jellification powder |
| DSF\% | Percentage Deterioration of the Swallowing Function |
Preface

The thesis is based on the following papers, referred to in the text by their Roman numerals.


Permissions have been given by Wiley & Sons and by SAGE publishing to reprint Papers I, II and IV from Acta Neurologica Scandinavica, and from Annals of Otology, Rhinology & Laryngology, according to the copyright transfer agreements.
Sammanfattning på svenska

Parkinsons sjukdom är en neurologisk progredierande sjukdom som främst kännetecknas av problem med motorikstörningar. Skakningar i händerna, muskelstelhet, förlängsammade rörelser och nedsatt kroppsstabilitet är typiska symptomblock som förekommer vid Parkinsons sjukdom. Förutom motoriska rörelsestörningar föreligger ofta ytterligare sjukdomsrelaterade svårigheter såsom viktförändring, depression och påverkan på tal-, röst- och sväljfunktion.

Den normala sväljningen består av fyra faser, varav en berör svalgets funktion. Denna avhandling fokuserar främst på svaljpåverkan som beror på svårigheter i svalget exempelvis när mat svaljs fel ner i luftstrupen eller ligger kvar i svalget efter sväljningen. Sväljsvårigheter är vanliga hos äldre människor. Mat som svaljs fel och hamnar i luftstrupen kan orsaka lunginflammation med ökad risk för dödlighet.

Under sjukdomsförloppet får fyra av fem patienter med Parkinsons sjukdom sväljsvårigheter. I början av sjukdomsförloppet kan symptomen vara ganska lindriga, ibland är inte ens patienten själv medveten om sina sväljsvårigheter. Även lindriga sväljsvårigheter kan ha negativ påverkan på livskvaliteten för såväl patienten som anhöriga, då måltiderna kan präglas av rädsla och social stress. Genom att använda specialanpassade frågeformulär såsom Swallowing Quality of Life (SWAL-QOL) formuläret kan vi vetenskapligt beskriva hur sväljsvårigheterna påverkar livskvaliteten. SWAL-QOL formuläret finns översatt till svenska.

Även om Parkinsons sjukdom inte går att bota kan symptomen ofta behandlas effektivt med hjälp av medicinering, vanligen används L-Dopa. Innan L-Dopa fanns tillgängligt användes neurokirurgi som behandling vid Parkinson’s sjukdom. När L-Dopa upptäcktes på 1950-talet minskade antalet kirurgiska behandlingarna. En oönskad effekt av långvarigt bruk av L-Dopa är att effekten av medicineringen på patientens parkinsonism successivt avtar, och efterhand leder till svårbehandlade biverkningar.

Samtidigt som ny grundvetenskap under 1980- och 1990-talet visade hur de olika delarna av basala ganglierna samverkade med övriga delar av centrala nervsystemet inleddes försök med neurokirurgisk behandling vid Parkinsons sjukdom. Djup hjärnstimulering (DBS) utvecklades då till ett behandlingsalternativ för patienter med Parkinsons sjukdom. Vid DBS förs en tunn stimuleringselektrod in i specifika målområden i hjärnan under tredimensionell, s.k. stereotaktisk teknik. Elektroden kopplas till en inopererad stimulator (ibland kallad "neuro-pacemaker"). Stimulatorn
levererar en svag elektrisk ström till olika delar av hjärnan och kan på så vis påverka de motoriska symptomen vid Parkinsons sjukdom. Med hjälp av en yttre manövreringsenhet kan stimuleringen justeras och slås av och på vid behov.

Det vanligaste målet för elektroden är subthalamuskärnan, men även den närliggande kaudala delen av zona incerta används vid DBS-kirurgi. Stimulering av dessa målområden har vid Parkinsons sjukdom visat sig ge god effekt på kroppsmotoriken, medan effekten på andra motoriska funktioner såsom tal- och sväljefunktionen, inte är lika väl studerad. Vissa studier har visat att sväljefångriggorna kan uppkomma i samband med DBS medan andra studier funnit en viss förbättring av sväljefunktionen efter DBS. Målet med denna avhandling har därför varit att undersöka hur DBS i subthalamuskärnan och i kaudala zona incerta påverkar såväl sväljefunktionen som sväljningsrelaterad livskvalitet hos personer med Parkinsons sjukdom. Vidare undersöktes också hur DBS påverkar kroppsvikt, hantering av bestick och talfunktionen.

Avhandlingen baserar sig på fyra delarbeten och inkluderar elva patienter med DBS i subthalamuskärnan och sjutton patienter med DBS i kaudala zona incerta. Dessa patienters sväljefunktion studerades före liksom 6 och 12 månader efter DBS-operation, såväl kliniskt med fiberoptisk videoteknik, som med egenrapportering av självskattad sväljefunktion. Nio personer utan Parkinsons sjukdom fungerade som kontrollgrupp vid självskattningen av den sväljningsrelaterade livskvaliteten.

Resultatet visade att DBS, i subthalamuskärnan eller i kaudala zona incerta, inte hade några negativa effekter på sväljefunktionen hos patienterna. Patienterna med DBS i subthalamuskärnan skattade sin sväljefunktion som förbättrad. Patienterna med DBS i kaudala zona incerta skattade sin sväljningsrelaterade livskvalitet som likartad före och efter DBS operationen.

Patienternas skattningar av livskvaliteten var i princip likställd kontrollgruppen men patienterna beskrev flera sväljsymtom och större bördä jämfört med kontrollgruppen. Endast lindriga till måttliga sväljefångriggorna förekom i patientgruppen.

Resultaten överensstämmer med slutsatser från andra studier där man undersökt sväljefunktionen vid DBS i subthalamuskärnan. Ett bifynd i avhandlingen var att DBS i kaudala zona incerta kan bidra till viktokning och ge lindriga talsvårigheter. Förmågan att hantera bestick förbättrades efter DBS.
Det är av betydelse vid tolkningen av avhandlingens resultat att beakta det faktum att antalet patienter är lågt och att de rekryterade patienterna hade varit sjuka under en ganska kort tid. Vi vill betona betydelsen av fortsatta studier i ämnet och att i framtiden inkludera fler patienter, följa sväljfunktionen under en längre tidsperiod, samt observera patienter med mer avancerad parkinsonism.

Slutsatsen av denna avhandling är att Parkinsononpatienter med lindriga sväljvårigheter kan genomgå DBS behandling, utan att riskera försämrad sväljfunktion. Detta är viktig information att delge patienterna inför ställningstagande till DBS operation.
Introduction

Parkinson’s disease

Parkinson’s disease (PD) is one of the most common neurodegenerative diseases in Europe\(^1\). The condition is named after James Parkinson who was the first to describe the disease in 1817\(^2\). The prevalence rate is 571/100 000, and rising with increasing age\(^3\). There is a predominance of male patients\(^3,4\) although gender homogeneity in PD has been reported\(^5,6\). The specific cause of the disease remains unknown but the progression of PD is due to a successive loss of dopamine producing neurons in the substantia nigra\(^7\). Genetic as well as environmental risk factors have been linked to PD\(^8–10\).

The cardinal signs are bradykinesia, resting tremor in extremities, rigidity, and postural instability\(^11,12\). The symptomatology of PD is very heterogeneous, with classic motor symptoms as well as a range of secondary motor and non-motor features with significant clinical impact\(^7,11,12\). Sialorrhea, weight change, constipation and, depression are examples of non-motor features. Speech problems, dystonia and dysphagia are considered to be secondary motor features. Among these signs, extra attention must be given to swallowing problems as this comorbidity gives a high mortality rate\(^11,13\).

Swallowing function

Swallowing in healthy persons is a complex sensory-motor process, which includes voluntarily induced motor acts, pre-programmed and reflexogenically modified muscular activation patterns, as well as autonomically induced propulsive motor events. The act of swallowing is commonly divided into four different phases.

*The four swallowing phases*

The **first phase** is the *pre-oral phase* defined by the ability to sit and eat, the state of hunger, and feelings towards eating. Disorders in the first swallowing phase are characterized by difficulties with handling cutlery, reduced meal time pleasure or anxiety related to eating or swallowing\(^14\).

The **second phase** is the *oral phase*, which begins when the bolus enters the mouth. This phase is defined by the processing of food by the tongue and teeth through repetitive elevations of the tongue, routing of the bolus to the back of the mouth and mixing it with saliva\(^15–17\). Oral phase swallowing disturbances include leakage through lips, poor bolus formation, lingual
tremor, repetitive tongue rolling, delayed oral transit, or preswallow spillage of bolus\textsuperscript{18–20}; the last phenomenon occurring when the bolus reaches the pharynx before the airway entrance is protected.

The \textbf{third phase} is the \textit{pharyngeal phase} starting when the bolus passes the pharyngeal pillars\textsuperscript{15}. This phase of swallowing is not under voluntary control. The food is transported from the level of the pharyngeal pillars through the pharynx and into the esophageal tube via the upper esophageal sphincter. As pharyngeal swallowing is triggered, several vital and protective mechanisms are simultaneously initiated. Breathing is inhibited, the velopharyngeal port is closed, and the hyoid and the larynx are elevated in order to protect the airway. Throughout the pharyngeal bolus passage, the larynx is elevated, and the airway is protected by the tilted epiglottis and the adducted true and false vocal cords.

Pharyngeal swallowing problems include aspiration, penetration, and pharyngeal residue\textsuperscript{19}. If penetration occurs, the bolus enters the airway and reaches the vocal cords. Aspiration is defined as the passage of bolus through the airway below the vocal cords. Aspiration is associated with high morbidity and mortality through its role in the development of pneumonia. Pharyngeal residue occurs when bolus remains in the valleculae or piriform sinuses post swallowing and is associated with increased risk for secondary penetration and aspiration\textsuperscript{21,22}.

The \textbf{fourth phase} is the \textit{esophageal phase}, which occurs as the bolus passes the upper esophageal sphincter and enters the esophageal tube. The bolus is carried to the stomach by the peristaltic movements of the oesophagus and gravity. As the bolus reaches the bottom of the oesophagus the lower esophageal sphincter relaxes and the bolus enters the stomach. The transition from the upper esophageal sphincter to the stomach takes approximately 6 seconds\textsuperscript{23}. The esophageal phase is controlled by the autonomic nervous system. Swallowing problems may be defined clinically as prolonged transition through the oesophagus, stasis of the bolus, and gastro-esophageal reflux\textsuperscript{22}.

This thesis focuses mainly on the pharyngeal phase, since it is associated with high mortality and morbidity in PD, although some additional aspects from the other phases are also addressed.
Assessment of swallowing function

The efficacy of swallowing function can be assessed clinically, with instrumental methods, or by the use of self-report scales. The most common instrumental methods are Video Fluoroscopic Swallowing Study (VFSS) and Fibreoptic-Endoscopic Evaluation of Swallowing (FEES)\textsuperscript{24,25}. VFSS is also known as radiological modified barium based examination of functional swallowing. The swallowing procedure is followed in real-time throughout the four different phases of swallowing\textsuperscript{24}. In a FEES examination a small flexible endoscope is transnasally inserted into the pharynx, allowing the larynx to be inspected from above during a predefined test meal. In both FEES and VFSS examinations the clinician can directly observe pharyngeal swallowing problems such as penetration, aspiration, preswallow spillage, and pharyngeal residue\textsuperscript{24,25}.

Patient reported outcome

As a complement to the interpretation by clinicians, patients should be offered the opportunity to give their own opinion of the quality of their swallowing act. Several studies have shown that evaluations through clinical examinations by physicians, as well as objectively documented assessments by FEES and VFSS, clearly deviate from what is reported by the patients themselves \textsuperscript{26–31}. Prevalences of swallowing problems are generally lower in patient ratings compared to evaluations by clinician or instrumental examinations. Patients claiming to have no swallowing problems can be found to have significant problems in clinical examinations\textsuperscript{32}. The use of validated swallowing questionnaires should be preferred ahead of unstructured swallowing questions\textsuperscript{33,34}. Despite this, and the fact that patients’ feelings regarding swallowing problems have been found to have a substantial effect on eating habits and well being, only limited attention has been given to patients’ self-reports\textsuperscript{35,36}.

Several validated self-report scales have been developed over recent years\textsuperscript{33,34}. Examples of self-report scales focusing on health-related quality of life (QOL) in oropharyngeal dysphagia are the dysphagia handicap index (DHI)\textsuperscript{37}, the M.D. Anderson Dysphagia Inventory (MDADI)\textsuperscript{38} and the Swallowing Quality of Life (SWAL-QOL)\textsuperscript{39,40}. Among these, the SWAL-QOL is the most preferable self-report scale, addressing swallow-specific QOL in progressive neurological disorders like PD\textsuperscript{34}. 
**Parkinson’s disease and swallowing problems**

Swallowing problems are common in PD, and the consequences of dysfunctional oropharyngeal swallowing are severe, since swallowing difficulties increase the risk of aspiration pneumonia which is the comorbidity with the highest mortality rate in PD\textsuperscript{11,13}.

The prevalence of swallowing problems in PD, measured by instrumental examination tools, is 82\%±5\%, while the prevalence of self-perceived dysphagia in community living PD patients is 35\%±6\%\textsuperscript{26}. It has been estimated that close to 70% of patients with PD show abnormalities in the oral phase\textsuperscript{41}, due to hypokinetic movements of the tongue and the palatal muscles. Wet voice quality and post-swallow cough have been found in 40\% of PD patients\textsuperscript{41}. Decreased suction pressure\textsuperscript{42}, prolongation of larynx movement and oral-pharyngeal transit times, as well as problems with initiation of the swallowing procedure have been reported\textsuperscript{30}.

Silent aspiration and post-swallow pooling are more common in PD patients than in healthy controls\textsuperscript{27,43}, but patients in early stage PD may also have a swallowing function comparable to healthy controls\textsuperscript{44}. Swallowing deterioration is common in the later stages of PD, but reports diverge when it comes to correlating swallowing difficulties with disease duration or severity of PD. Some studies report significant associations\textsuperscript{29,45}, while others do not\textsuperscript{27,42,46}. A possible reason for this could be adaptive cerebral changes, compensating for the deficient motor pathways in some non-dysphagic PD patients\textsuperscript{47}.

**Parkinson’s disease and swallow-specific quality of life**

Although it is well known that PD patients suffer from swallowing problems, very little attention has been paid to the impact of swallowing problems on their everyday lives. Miller et al. performed semi-structured interviews and found several factors affecting QOL in patients\textsuperscript{48}. Fear of choking, long eating durations, food selection, feelings of guilt, and concerns about caregiver burden were the most important factors. Miller et al. also concluded that even mild swallowing problems have consequences for patients and their caregivers\textsuperscript{48}.

A few studies that have incorporated the SWAL-QOL questionnaire are available and two of them report lower swallow-specific QOL in PD patients compared to age-matched controls \textsuperscript{49–51}. Leow et al. present separate SWAL-QOL scores for patients in early and in late stage PD. Patients in early stage PD report better swallow-specific QOL regarding ‘Food selection’, ‘Eating
duration’ and ‘Eating desire’\textsuperscript{50}. As swallowing problems have a profound impact on QOL, it is important to consider swallowing function when choosing treatments for PD.

**Treatment for Parkinson’s disease**

Levodopa (L-Dopa) has been the standard treatment for the cardinal symptoms of PD since the first trials in the 1960s\textsuperscript{52,53}. L-dopa has a recognized effect on general motor symptoms but there is still a great need for research regarding treatment of secondary and non-motor features in PD\textsuperscript{11,54,55}. The effect of L-dopa on swallowing function is reported as divergent, some studies have shown positive effects\textsuperscript{20,31}, while others have reported deterioration\textsuperscript{20,56}. Meneze and Melo\textsuperscript{57} performed a systematic review of the effect of L-dopa on swallowing function and concluded that there is no strong evidence for a positive outcome on swallowing function with L-Dopa treatment\textsuperscript{57}. This conclusion has been questioned by Sutton\textsuperscript{58} who presents scientific data for a contrary statement. The truth probably lies somewhere in between, which is the conclusion of recently published data by Warnecke et al., demonstrating that about 50% of the study subjects with advanced PD had improved swallowing function with L-dopa compared to without L-dopa\textsuperscript{59}.

Besides L-dopa, there are also other pharmacological alternatives available like MAO-B inhibitors, dopamine agonists and anticholinergic agents\textsuperscript{60}. These pharmacological treatments are not discussed further in this thesis.

**Deep Brain Stimulation**

Deep Brain Stimulation (DBS) is a treatment alternative for patients with medically refractory PD. Stereotactic lesion surgery for treatment of PD and other movement disorders was introduced in the 1950s before the use of L-Dopa\textsuperscript{61}. When L-Dopa was introduced, the popularity of stereotactic surgeries decreased due to the effectiveness of the L-dopa\textsuperscript{54,61}.

During the 1980s and 1990s, the interest in different stereotactial surgeries increased again as the side-effects of long-term treatment with L-dopa, such as motor fluctuations and drug-induced dyskinesias, became evident\textsuperscript{54,62}. At this time point, the surgical and imaging techniques had been improved, as well as the understanding of PD\textsuperscript{54}. The re-evaluation of Leksell’s posteroverentral palliodotomy by Laitinen et al. \textsuperscript{62} resulted in a world-wide revitalization of palliodotomy and stereotactic surgeries. Following this, Pollak and Benabid conducted their pioneering work with the development of DBS technology, initially targeting the subthalamic nucleus (STN)\textsuperscript{63–65}. In
DBS surgery, electrodes are implanted into the target by a stereotactic procedure. A programmable pulse generator is placed subcutaneously in the subclavicular area of the patient. The stimulation is adjusted carefully after surgery to minimize adverse effects and maximize the benefits of DBS. The DBS stimulation can be turned off and on by the patient via a patient operated programming device. The reversibility provided by the stimulation control is a great benefit compared to the previously used permanent stereotactic lesions.

The mechanisms underlying the therapeutic effects of DBS are still under debate. It is hypothesized that DBS affects both the stimulated nucleus and the surrounding fibre pathways. Both excitatory and inhibitory effects are present and there is an effect on the entire basal ganglia thalamocortical network.

Some PD symptoms, such as tremor and rigidity, are particularly responsive to DBS, while the effect on axial symptoms is uncertain and can emerge days or weeks after DBS surgery. The positive effects of DBS on motor symptoms and health related QOL in PD have been well documented. DBS in the STN (STN DBS) improves motor function during the ‘medication off’ state when the motor symptoms are most pronounced. Clinically, the patient experiences a higher and more reliable level of motor functioning. STN DBS also shortens the ‘OFF’ periods with troublesome symptoms and reduces dyskinesias. The QOL of PD patients is improved by STN DBS, as defined by improved activities of daily life, mobility, emotional well-being and reduced stigma.

Although the most common target for DBS is the STN, an alternate target is the posterior subthalamic area (PSA). Treatment with PSA DBS or caudal zona incerta DBS (cZI DBS) shows similar positive effects on motor functions as STN DBS. A non-randomized sequential study with 36 subjects has reported better limb outcomes with cZI DBS compared to STN DBS.

In addition to the positive outcomes there are a range of putative adverse effects of DBS. According to the review by Kleiner-Fisman, the most common negative effects related to STN stimulation were dysarthria, weight gain and depression. Other side effects were hypophonia, sialorrhea, and dysphagia. As for cZI DBS, there are no review articles on adverse events but blurred vision and dysarthria have been reported.

Weight gain is a common side effect of STN DBS. Macia et al. and Barichella et al. reported increased weight in 100% of the PD patients with
STN DBS. The reason for the weight gain is discussed and a possible decrease in the patients’ energy expenditure\textsuperscript{97}, as well as an increased sensitivity to food reward cues due to STN DBS, which would increase the inclination for eating, were mentioned\textsuperscript{98}. There are to date no reports on how cZI DBS affects body weight.

**Swallowing function and Deep Brain Stimulation**

The effect of STN and cZI DBS on swallowing function has been studied, but the reported results are ambiguous. To date, four studies on STN DBS and swallowing function have been reported, in which instrumental measures like FEES or VFSS were used\textsuperscript{99–102}.

The most recent study was conducted by Troche et al.\textsuperscript{102}. A total of 14 patients with unilateral STN DBS were included in the retrospective study. All VFSS examinations were performed with L-dopa medication on, and patients also rated their swallow-specific QOL with the SWAL-QOL questionnaire. Compared to baseline, these patients had worsened Penetration-Aspiration scale scores at 6 months after surgery. The study did not include a comparison between stimulation on versus stimulation off. The swallow-specific QOL was not affected after 6 months with STN DBS. The scores from the SWAL-QOL questionnaire were not presented as a score between 0 and 100% and this precludes comparison to other SWAL-QOL studies.

In the study by Ciucci et al., the swallowing function of 14 patients with STN DBS was assessed by VFSS with and without STN DBS stimulation (on medication)\textsuperscript{99}. The authors did not state whether the stimulation was uni- or bilateral. Their results indicate that the patient group had mild swallowing problems and that swallowing was somewhat improved when DBS stimulation was turned on\textsuperscript{99}.

The retrospective study by Lengerer et al. included 18 patients with bilateral STN DBS\textsuperscript{101}. Swallowing function was evaluated by VFSS at 20 months after DBS surgery with and without STN stimulation. The authors reported small improvements due to STN DBS, but concluded that the enhancements were too small to have clinical relevance\textsuperscript{101}.

Silbergleit et al. examined swallowing function with VFSS and the self-report questionnaire DHI in 14 PD patients with bilateral DBS\textsuperscript{100}. Non-significant trends regarding improved swallowing response and oral preparation with DBS were seen in the medication off condition. The self-report results indicated a self-perceived improvement in swallowing function 3 and 12
months after DBS surgery. The authors’ conclusion was that ‘bilateral STN-
DBS does not substantively impair swallowing in PD’\textsuperscript{100}.

In addition to these studies there is a recent case report, in which Troche et
al. described severe swallowing problems in a single PD patient with
unilateral right side STN and another unilateral lead in the left side globus
pallidus internus (GPi)\textsuperscript{103}. The authors reported severe swallowing problems,
which were reduced after reprogramming of the DBS, guided by repeated
VFSS evaluations, to ensure best possible airway protection while
maintaining control of tremor and bradykinesia\textsuperscript{103}.

The results of the four published studies on swallowing function and STN
DBS do not clarify how STN DBS affects swallowing safety\textsuperscript{99–102}. Two studies
with bilateral STN DBS conclude that DBS does not have negative
effects\textsuperscript{100,101}, while one study with unilateral STN DBS reports a negative
outcome with increased aspiration and penetration\textsuperscript{102}.

To date, there are no reports on the effect of cZI DBS on swallowing
function. The studies included in this thesis are the first that address
swallowing safety in cZI DBS.
Purpose of the study

The purpose of this thesis was to elucidate possible effects of DBS on swallowing outcomes and to increase the understanding of STN and cZI DBS on pharyngeal swallowing function and on subjective swallow-specific QOL perceptions in patients with PD. The aim was to assess the effect of STN and cZI DBS on swallowing 6 and 12 months postoperatively, and to evaluate swallowing related non-motor and secondary motor features such as body weight changes, sialorrhea and speech problems.

The thesis addresses four interrelated questions:

1) Do STN and cZI DBS have an effect on pharyngeal swallowing parameters?

2) Do STN and cZI DBS have an effect on self-estimated swallowing function?

3) Does cZI DBS have an effect on swallowing related secondary and non-motor features such as body weight, sialorrhea and speech problems?

4) Does cZI DBS have an effect on patients’ swallow-specific QOL perceptions?
Materials and methods

The four studies in this thesis included consecutive PD patients selected for surgical treatment by the neurosurgical team at Umeå University Hospital, according to best clinical practice and based on internationally accepted inclusion and exclusion criteria for DBS (CAPSIT-PD)$^{104}$. The cZI patients were also included in a larger research trial at Umeå University Hospital examining the overall outcomes of cZI DBS. Study participants were recruited over the period 2005-2013. An overview of the studies included in this thesis is provided in Table 1.

Table 1 Overview of the papers in the thesis

<table>
<thead>
<tr>
<th>Paper</th>
<th>Properties</th>
<th>Material and Methods</th>
<th>6 months postoperatively</th>
<th>12 months postoperatively</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paper I</td>
<td>11 patients with STN DBS. Median age: 61 years. 8 male, 3 female.</td>
<td>Medication on and off: FEES, VA-scale, UPDRS-II</td>
<td>Stimulation on and off: FEES, VA-scale</td>
<td>Stimulation on and off: FEES, VA-scale</td>
</tr>
<tr>
<td>Paper II</td>
<td>8 patients with cZI DBS. Median age: 63 years. 6 male, 2 female.</td>
<td>Medication on and off: FEES, VA-scale, UPDRS-II</td>
<td>Stimulation on and off: FEES, VA-scale</td>
<td>Stimulation on and off: FEES, VA-scale</td>
</tr>
<tr>
<td>Paper III</td>
<td>14 patients with cZI DBS. Median age: 57 years. 12 male, 2 female.</td>
<td>Medication on: QOL-questions</td>
<td>Stimulation on: QOL-questions</td>
<td>Stimulation on: QOL-questions</td>
</tr>
<tr>
<td>Paper IV</td>
<td>9 patients with cZI DBS. Median age: 53 years. 7 males, 2 females. 9 controls included.</td>
<td>Medication on and off: UPDRS-III</td>
<td>Stimulation on: SWAL-QOL, VA-scale</td>
<td></td>
</tr>
</tbody>
</table>


The inclusion criteria were based on clinical grounds for DBS surgery according to assessment of overall motor function and no consideration was given to swallowing status. Exclusion criteria were cognitive impairment, deep depression, age above 75 years, medical conditions prohibiting operation, alcohol or substance abuse over the last 5 years, brain atrophy, as well as practical reasons that ruled out the defined follow-up procedures. PD patients with tremor dominant symptoms as well as non-tremor dominant symptoms were included. Idiopathic PD diagnosis was made based on the
Written informed consent was provided by the patients, and the studies were conducted in accordance with the World Medical Association’s ‘Declaration of Helsinki’. Ethical approval for the studies was given by the regional Ethics boards in Umeå and in Gothenburg (nos. 08-093M, 08-009M and 846-15). Patients were followed prior to DBS surgery, then 6 and 12 months postoperatively. At each time point, data were collected from instrumental, as well as patients’ self-reports.

Participants

Paper I – STN DBS
The study in Paper I included eleven consecutive PD patients. Detailed patient characteristics are provided in Table 2. Implantations in the STN were uni- or bilateral. None of the patients in this study group used anticholinergic medications. Video material from FEES was analysed from eight of the eleven patients. Data from three patients were included only in the analysis of patients’ self-assessments, due to incomplete or missing FEES video material.

Table 2 Characteristics of PD patients with STN DBS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PD patients (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td>41-72</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>6.5</td>
</tr>
<tr>
<td></td>
<td>1-13</td>
</tr>
<tr>
<td>UPDRS-III medication off preoperatively</td>
<td>39.0</td>
</tr>
<tr>
<td></td>
<td>19-57</td>
</tr>
<tr>
<td>UPDRS-III medication on preoperatively</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>4-57</td>
</tr>
<tr>
<td>LEDD (mg)</td>
<td>919</td>
</tr>
<tr>
<td></td>
<td>300-2145</td>
</tr>
<tr>
<td>Gender female/male (n/n)</td>
<td>3/8</td>
</tr>
<tr>
<td>Uni/bilateral stimulation (n/n)</td>
<td>5/6</td>
</tr>
<tr>
<td>Indication for surgery</td>
<td>On-off fluctuations (2), tremor (8), wearing off (1)</td>
</tr>
</tbody>
</table>

PD: Parkinson’s Disease. STN DBS: Subthalamic Nucleus Deep Brain Stimulation. LEDD: L-dopa Equivalent Daily Dose. UPDRS-III: Motor part of Unified Parkinson’s Disease Rating Scale, lower scores for better function.

Paper II and Paper III – cZI DBS
A total of 23 patients were evaluated for inclusion in the study groups in Papers II and III. Fourteen of the PD patients were prospectively included in the study group in Paper III, and eight of those were also included in the study group in Paper II, while the remaining nine patients were excluded.
(See figure 1). Reasons for exclusion were; poor outcome of the neuropsychiatric examination (n=5), unilateral DBS (n=2) and complications (n=1). One patient declined to participate in the postoperative follow up. A detailed outline of the patient characteristics of the two study groups is provided in Table 3.

**Figure 1. Outline of the included and excluded patients in the study groups of Papers II and III. cZI: caudal zona incerta.**

**Table 3. Patient characteristics at baseline. Study groups in Papers II and III**

<table>
<thead>
<tr>
<th>Excluded or declined to participate (n=9)</th>
<th>Study group in Paper II (n=8)</th>
<th>New sample in Paper III (n=6)</th>
<th>Study group in paper III Pooled from Paper II and new sample (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>median (range)</td>
<td>68 (60-74)</td>
<td>62 (49-71)</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>6 (1-20)</td>
<td>6 (2-13)</td>
<td>8 (4-13)</td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td>24.3 (18.7-30.9)*</td>
<td>26.1 (18.4-30.9)</td>
<td>25.0 (23.0-38.4)</td>
</tr>
<tr>
<td>UPDRS-III off med</td>
<td>43 (18-58)*</td>
<td>36 (29-58)</td>
<td>41 (18-53)*</td>
</tr>
<tr>
<td>UPDRS-III on med</td>
<td>16 (10-42)*</td>
<td>20 (10-42)</td>
<td>23 (8-45)*</td>
</tr>
<tr>
<td>LEDD (mg)</td>
<td>1015 (606-1421)*</td>
<td>1013 (300-1997)</td>
<td>1271 (0-2412)</td>
</tr>
<tr>
<td>Hoehn&amp;Yahr</td>
<td>No data</td>
<td>2.5 (1.5-2.5)</td>
<td>2 (2-2)**</td>
</tr>
<tr>
<td>Gender female/male (n/n)</td>
<td>2/7</td>
<td>2/6</td>
<td>0/6</td>
</tr>
<tr>
<td>Anticholinergic medication</td>
<td>none</td>
<td>none</td>
<td>1 patient</td>
</tr>
<tr>
<td>Indication for surgery</td>
<td>No available data</td>
<td>tremor (5), on-off fluctuations (2), rigidity/bradykinesia (1)</td>
<td>tremor+/=wearing off (4), on-off fluctuations (2)</td>
</tr>
</tbody>
</table>

BMI: Body Mass Index. UPDRS-III: Motor part of Unified Parkinson's Disease Rating Scale, lower scores for better function, LEDD: Levodopa Daily Equivalent Dose, *Data missing from one patient **Data missing from three patients
All patients had bilateral DBS in cZI. Pre-, as well as post-operative CT-scans ensured that the electrode location was within the cZI-target. Stimulation frequencies were between 125 and 160Hz for all patients.

**Paper IV - Swallow-specific quality of Life**

Eighteen patients prospectively selected to cZI DBS were preoperatively screened for inclusion in the study group in Paper IV (Figure 2). Patient characteristics from the nine patients included in the study group are provided in Table 4. Six patients from Paper IV were also included in the study group in Paper III. Nine of the selected patients were excluded due to poor performance in the neuropsychiatric examination (n=3), use of duodopa instead of surgery (n=1), unilateral DBS (n=3), alternative DBS target (n=1), or declined to participate in the 12 months follow up (n=1). All patients in Paper IV were selected to bilateral cZI DBS, and pre- as well as post-operative CT-scans ensured that the electrode location was within the cZI-target. Stimulation frequencies were between 125 and 160Hz for all patients.

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Median (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53 (40-70)</td>
</tr>
<tr>
<td>Gender female/male (n/n)</td>
<td>2/7</td>
</tr>
<tr>
<td>Married or cohabitant</td>
<td>7 patients</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>10 (5-13)</td>
</tr>
<tr>
<td>UPDRS-III medication off</td>
<td>40 (18-52)</td>
</tr>
<tr>
<td>UPDRS-III medication on</td>
<td>17 (6-45)</td>
</tr>
<tr>
<td>Hoehn&amp;Yhar</td>
<td>2+ (2.0-2.5)</td>
</tr>
<tr>
<td>LEDD (mg)</td>
<td>1227 (300-1746)</td>
</tr>
<tr>
<td>Stimulation frequencies (Hz)</td>
<td>125-160 Hz</td>
</tr>
<tr>
<td>Indication for surgery</td>
<td>On-off fluctuations (4), tremor and wearing off (5)</td>
</tr>
</tbody>
</table>

PD: Parkinson’s Disease. LEDD: L-dopa Equivalent Daily Dose. UPDRS-III: Preoperative scores from motor part of Unified Parkinson's Disease Rating scale, lower scores for better function. Hoehn&Yhar: Scores 1-5p with lower score for better function. *Data missing from three patients
A group of nine controls without PD were included in the study, consecutively recruited from patients at the Department of Otorhinolaryngology at Sahlgrenska University Hospital in Gothenburg, Sweden. The controls were matched to the PD patients for gender, and were of comparable marital status, and age (± 3 years). The reasons for their visits to the clinic were chronic tonsillitis, vertigo, extirpation of nevus, snoring, salivary stones or chronic rhino sinuitaris.

**Procedures and data material**

The studies in this thesis were based on equal instrumental technology and had similar procedures and materials. Table 1 presents the time points and the material for the studies. Patients were followed prior to DBS surgery, then 6 and 12 months postoperatively. Preoperatively, evaluations were done with ‘medication off’ (medication withheld for 12 hours or overnight) and ‘medication on’ (a L-dopa test-dose 1.5 times the ordinary morning dose of medication for Parkinson’s disease). Postoperative evaluations at 6 and 12 months after DBS were performed with ‘stimulation off’ and ‘stimulation on’.

Postoperatively, all examinations were done with optimal ordinary dosage of medication for Parkinson’s disease. A study design that incorporated examinations without L-dopa medication after DBS-surgery would have been methodologically preferable, as it would have provided the opportunity of selectively assessing the effect of the DBS stimulation alone. However, such a study design was not considered to be ethically justifiable, as the patients performed a range of tests over two days, and the discomfort associated with the medication off state is considerable. It was necessary to limit the number of study days off medication after surgery, due to the overall number of tests performed, and the time needed to complete them.

The procedure and material was the same for Papers II, and I except for the inclusion of the QOL related swallowing questions in Paper II. In Paper III we used partly the same material as in Paper II, but data regarding body mass index (BMI) and specific items from UPDRS part II were added. The data analyses were also optimized to ensure higher statistical power. Paper IV focused on the patients’ own experience, through the SWAL-QOL questionnaire and data from a visual analogue scale (VA-scale).

*Evaluation of the swallowing function*

Swallowing function was evaluated using FEES, and an Olympus ENF P transnasal flexible endoscope and a Wolf endocam 5502. In later examinations (part of study in Paper III), an Olympus ENF VH flexible video endoscopy combined with an Olympus CV -170 light source system was used.
All video recordings were randomized for order and anonymized before the data assessment.

The FEES examination included one solid and four liquid consistencies. The consistencies were 50 ml water (C1), 50 ml water with 5 ml jellification powder (C2), 50 ml water with 10 ml jellification powder (C3), and 50 ml water with 15 ml jellification powder (C4). The solid consistency (C5) was a biscuit with a smear of C4 on top. All food was dyed with green colouring. Patients were given the food according to a standardized procedure and the bolus size was one tablespoon (15 ml).

A predefined swallowing protocol was used to evaluate swallowing in Papers I-III. The protocol included parameters for penetration/aspiration (0-7p) (Rosenbek’s Penetration-Aspiration scale\textsuperscript{107}, secretion (0-3p) (Secretion Severity scale\textsuperscript{108}), pharyngeal residue (0-1p), pharyngeal clearance (0-1p), and preswallow spillage (0-1p). Preswallow spillage was defined as any green bolus seen before white-out in the FEES. Pharyngeal residue was operationalized as residue in the piriform sinuses or valleculae after the swallow, and pharyngeal clearance as no residue after the swallow.

The Penetration-Aspiration scale and Secretion Severity scale were shifted so that the lowest possible score was 0 points. A mean score from the five different meal consistencies (C1-C5) was calculated separately for penetration/aspiration, secretion, pharyngeal residue, pharyngeal clearance, and preswallow spillage scores. This mean score was used in Paper I and II to examine the effect of STN DBS and cZI DBS. In Paper III, only data from the solid and liquid consistencies (C1 and C5) were used, and they were presented and analysed separately.

**VA-scale and QOL related swallowing questions**
In Papers I, II, and IV, a linear VA-scale was used to examine the patients’ own experiences of their swallowing function. The time points for the assessments are shown in Table 1.

The patients rated their swallowing function by putting a mark on the VA-scale (Figure 3). One end of the scale represents 100% swallowing function and the other endpoint represents total loss of swallowing function. In Papers I and II, the measure from the VA-scale was denoted ‘percentage deterioration of the swallowing function’ (%DSF). The %DSF was determined as 100% minus the evaluated score. In Paper IV the evaluated %measure was used and it was called VA-scale score. This term is also used in the kappa of this thesis.
In the study presented in Paper II, patients were invited to respond to a few QOL related swallowing questions in order to make more accurate judgements of their own swallowing experiences. The patients were asked if they had swallowing problems like weight loss, decreased mealtime pleasure, coughing when eating, need for consistency modification, affected swallowing function, sticky saliva/hemming or drooling. The responses were rated on a 4 point scale 0 = not at all, 1 = low, 2 = a lot, 3 = very much. At the time of the study in Paper II there was no Swedish version of SWAL-QOL available.

**BMI and UPDRS-items**

Height and weight of the patients were measured at the neurologic ward at the time of the swallowing examinations. In Paper III, BMI (kg/m²) was used as a measure of weight changes following cZI DBS.

Scores from the UPDRS were included for a comprehensive description of the included patients. Motor data from UPDRS-III are presented as patient characteristics in all four studies. Specific items from UPDRS-II were analysed in Paper III. These scores evaluating motor experience of daily life and items regarding sialorrhea, speech or swallowing problems, as well as difficulties with handling utensils, were extracted from the pre- and postoperative UPDRS-II evaluations in Paper III. An experienced DBS nurse administered all UPDRS assessments, using the labels; 0=normal; 1=slight problems; 2=mild problems; 3=moderate problems; 4=severe problems.

**Swallowing Quality of life**

The SWAL-QOL questionnaire is a self-administered questionnaire developed to address the impact of patients’ swallowing disorders on their QOL. The Swedish version of the questionnaire was used in Paper IV. This version was validated in 2011 by Finizia et al., and includes 44 statements and questions concerning swallowing, two questions concerning consistency modifications and one concerning general health.

Patients rate their swallowing symptoms by acknowledging how often during the last month they have had problems like ‘Choking when you eat food’, ‘Problems chewing’ or ‘Food sticking in your throat’. The response options
consist of a five-point Likert scale, ranging from one (representing ‘almost always’) to five (representing ‘never’).

The patients also answer questions like ‘In the last month, how often have the following statements been true for you because of your swallowing problem?’ by rating statements like ‘My swallowing problem frustrates me’ or ‘I’m worrying about getting pneumonia’, using a five point scale ranging from one (‘always true’) to five (‘never true’). A full list of the items in the questionnaire can be found in the review by Keage et al. 34

The items from the SWAL-QOL questions are grouped into ten subscales that address different domains: Food Selection (2 items), Burden (2 items), Mental Health (5 items), Social Functioning (5 items), Fear (4 items), Eating Duration (2 items), Eating Desire (3 items), Communication (2 items); Sleep (2 items); and Fatigue (3 items). Twenty-three items are summed to give a SWAL-QOL total score. The total score together with fourteen items comprise a ‘symptom’ scale score, for which lower scores indicate a higher symptom burden.

The SWAL-QOL scores from the Likert scales were linearly transformed to percentage ratings 0-100, in accordance with the validation by McHorney et al.39,40. The cut off-score for clinically relevant dysphagia has been suggested to be a total score of 86 or less, representing a decrease of 14 points from the maximum SWAL-QOL total score 110.

Data and statistical analysis

All descriptive statistics are presented with medians and ranges. All analyses were done using the SPSS software package. Two-tailed non-parametric tests were adopted in all studies, using a significance level of 5% for the null-hypothesis of no significance between groups. Friedman repeated measures test by ranks was used to test differences between multiple conditions over time (Papers I-III). Wilcoxon matched-pairs signed-ranks test was used for pairwise post hoc testing (Papers I-III). Spearman’s Rho (r_s) was used for tests of correlations between measures, and for tests of intra- and inter-rater reliability (Papers I-III).

Change over time regarding SWAL-QOL scores was analysed with Wilcoxon Signed Rank test and Sign test (Paper IV). The Wilcoxon matched-pairs signed-ranks test and the Sign test were also used for comparison between patients and controls, and the McNemar test was used for comparison between the PD group and controls with regard to marital status in Paper IV.
The magnitude of group differences was analysed using estimated effect size (Papers III and IV). Effect size was calculated according to the formula $r = \frac{z}{\sqrt{N}}$, where $N$ is the number of observation e.g. $N_{\text{observations}} = n_{\text{preop}} + n_{\text{postop}}$ or $N_{\text{observations}} = n_{\text{patients}} + n_{\text{controls}}$. This method complements standard significance testing, and generates standardized effect levels regardless of sample sizes. Values used for qualitative descriptions of effect size were ‘small’ ($r > .10$), ‘moderate’ ($r > .30$), ‘large’ ($r > .50$) and ‘very large’ effect size ($r > .70$).
Results

Paper I - STN DBS

The results from Paper I are summarized in Figure 4. Descriptive data from self-report on VA-scale, Penetration-Aspiration scale scores, and UPDRS III scores are shown in Table 5. Statistical testing and group medians are shown in Table 6.

Preoperatively, the subjective measure from the VA-scale was improved for test dose of L-dopa compared to medication off \((z=2.49, p=.01, r=.53)\). Swallowing parameters penetration/aspiration, secretion, pharyngeal residue, preswallow spillage, and clearance showed no changes between medication off and test dose of L-dopa \((p>.05)\).

Comparison between preoperative medication off and 6 months postoperative stimulation on revealed improvement in the subjective evaluation of swallowing function \((z=2.49, p=.01, r=.53)\). There were no differences between test dose of L-dopa and stimulation on at 6 and 12 months, \(p>.05\). No differences between pre- and postoperative conditions were observed regarding the swallowing parameters from the FEES.
Table 5 Individual data for Visual Analogue scale, Penetration-Aspiration scale and UPDRS-III scores

<table>
<thead>
<tr>
<th>Patient</th>
<th>Visual Analogue scale</th>
<th>Penetration-Aspiration scale</th>
<th>UPDRS-III</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preoperative</td>
<td>6m Postoperative</td>
<td>12m Postoperative</td>
</tr>
<tr>
<td></td>
<td>Med off</td>
<td>Test dose</td>
<td>Stim off</td>
</tr>
<tr>
<td>1</td>
<td>75</td>
<td>80</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>47</td>
<td>73</td>
<td>54</td>
</tr>
<tr>
<td>3</td>
<td>75</td>
<td>72</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>68</td>
<td>89</td>
<td>61</td>
</tr>
<tr>
<td>5</td>
<td>66</td>
<td>90</td>
<td>97</td>
</tr>
<tr>
<td>6</td>
<td>96</td>
<td>98</td>
<td>51</td>
</tr>
<tr>
<td>7</td>
<td>74</td>
<td>86</td>
<td>76</td>
</tr>
<tr>
<td>8</td>
<td>95</td>
<td>97</td>
<td>97</td>
</tr>
<tr>
<td>9</td>
<td>100</td>
<td>100</td>
<td>89</td>
</tr>
<tr>
<td>10</td>
<td>52</td>
<td>62</td>
<td>60</td>
</tr>
<tr>
<td>11</td>
<td>29</td>
<td>45</td>
<td>66</td>
</tr>
</tbody>
</table>

Mean: 70.6 | 81.1 | 76.4 | 86.9 | 71.5 | 82.6 | 0.5 | 0.2 | 0.1 | 0.1 | 0.4 | 0.2 | 39.6 | 20.4 | 18.6 | 14.9 | 30.4 | 18.2

Visual Analogue scale: 0-100%. The higher the score the better the function. Penetration-Aspiration scale score: 0-7p. The lower the score the better the function. UPDRS-III: Unified Parkinson’s Disease Rating Scale, the lower the score the better the function.

Table 6 Scores from swallowing evaluation and self-reported assessment of swallowing function. Median and range. Friedman test comparing differences among conditions. The lower scores the better the function for P/A, PS, Phr, CC and SS. The higher the score the better the function for the VA-scale.

<table>
<thead>
<tr>
<th>Median (Range)</th>
<th>Preoperative</th>
<th>6m Postoperative</th>
<th>12m Postoperative</th>
<th>Friedman test (n=8-11)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Med off</td>
<td>Test dose</td>
<td>Stim off</td>
<td>Stim on</td>
</tr>
<tr>
<td>P/A</td>
<td>0.1 (0.8)</td>
<td>0.0 (2.8)</td>
<td>0.0 (0.8)</td>
<td>0.0 (0.5)</td>
</tr>
<tr>
<td>PS</td>
<td>0.2 (0.6)</td>
<td>0.0 (0.2)</td>
<td>0.0 (1.0)</td>
<td>0.0 (0.4)</td>
</tr>
<tr>
<td>Phr</td>
<td>0.0 (1.0)</td>
<td>0.0 (0.8)</td>
<td>0.0 (1.0)</td>
<td>0.1 (0.7)</td>
</tr>
<tr>
<td>CC</td>
<td>0.0 (1.0)</td>
<td>0.0 (0.8)</td>
<td>0.0 (1.0)</td>
<td>0.1 (1.0)</td>
</tr>
<tr>
<td>SS</td>
<td>0.5 (2.0)</td>
<td>0.0 (2.0)</td>
<td>0.0 (3.0)</td>
<td>0.5 (3.0)</td>
</tr>
<tr>
<td>VA-scale</td>
<td>74.0 (71.0)</td>
<td>86.0 (55.0)</td>
<td>75.0 (46.0)</td>
<td>93.0 (34.0)</td>
</tr>
</tbody>
</table>

P/A: Penetration-Aspiration scale, 0-7p. Phr: Pharyngeal Residual, 0-1p. PS: Preswallow Spillage, 0-1p. CC: Clearance, 0-1p. SS: Secretions Severity scale, 0-3p. VA-scale: Visual Analogue scale; self-reported swallowing function, 0-100%.

Postoperatively, at 6 as well as at 12 months, the subjective measure from the VA-scale revealed a significant improvement with stimulation on compared to stimulation off (z=2.54, p=.01, r=.54). There were no differences between stimulation on and stimulation off for any of the swallowing parameters included in the FEES, p>.05.

Paper II - cZI DBS

The results from Paper II are summarized in Figure 5. The outcome from the statistical tests and medians for the specified test conditions are provided in Table 7. Brackets mark significant post-hoc differences.
Preoperatively, no significant changes were found between medication off and test dose of L-dopa for any of the swallowing parameters (p>.05). Aspiration was not observed in any of the patients.

Comparisons between preoperative test dose of L-dopa and 6 months postoperative stimulation on and stimulation off conditions showed a postoperative improvement regarding preswallow spillage in both on and off stimulation conditions (z=-2.27, p=.02 and r=-.57, z=-2.047, p=.04 and r=-.51, respectively).

At 6 months after DBS surgery, no differences between stimulation off and stimulation on, p>.05 (medication on) were seen for any of the swallowing parameters. At 12 months after DBS surgery, there was more preswallow spillage in the stimulation on condition compared to the stimulation off (z=2.070, p=.04, r=.52). At 12 months postoperatively, there were no other differences regarding the swallowing parameters (p>.05).

**Self-assessments**

The self-report on the VA-scale showed no differences between the testing conditions (Table 7). Likewise, the responses to the QOL related swallowing questions were similar across the testing conditions (Table 8).
The findings from Paper I are visualized in Figure 6. Descriptive data on swallowing parameters are seen in Table 9, and UPDRS scores for secondary and non-motor features are summarized in Table 10. CZI DBS did not have an effect on the swallowing parameters penetration/aspiration, pharyngeal residue or preswallow spillage (p>.05). The median BMI score was increased with 1.1kg/m² at 12 months after cZI DBS surgery and the median increase in weight were +3.0kg after 12 months with cZI DBS. Figure 7 illustrates the distribution of patients in different BMI categories.

**Table 7** Swallowing evaluation scores (averaged over the five consistencies) and self-reported assessment of swallowing function. Group median and range are shown for each measure with results of Friedman test comparing differences between conditions. Figures marked in bold show significant differences. Brackets show post-hoc differences. The lower scores the better the function for P/A, Phr, PS, PS, CC and SS. The higher the score the better the function for VA-scale.

<table>
<thead>
<tr>
<th></th>
<th>Preoperative Med off</th>
<th>6m Postoperative Stim off</th>
<th>12m Postoperative Stim on</th>
<th>Friedman test (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P/A</td>
<td>0.2 (2.4)</td>
<td>0.2 (1.4)</td>
<td>0.3 (1.8)</td>
<td>2.66 p=.75</td>
</tr>
<tr>
<td>Phr</td>
<td>0.6 (1.0)</td>
<td>0.6 (1.0)</td>
<td>0.7 (1.0)</td>
<td>5.06 p=.41</td>
</tr>
<tr>
<td>PS</td>
<td>0.6 (1.0)</td>
<td>0.6 (0.8)</td>
<td>0.7 (1.0)</td>
<td>13.83 p=.01</td>
</tr>
<tr>
<td>CC</td>
<td>0.5 (1.0)</td>
<td>0.7 (1.0)</td>
<td>0.7 (1.0)</td>
<td>5.25 p=.39</td>
</tr>
<tr>
<td>SS</td>
<td>0.5 (2.0)</td>
<td>1.0 (2.0)</td>
<td>0.5 (1.0)</td>
<td>12.09 p=.03</td>
</tr>
<tr>
<td>VA-scale</td>
<td>77.5 (98.0)</td>
<td>76.5 (40.0)</td>
<td>85.5 (22.0)</td>
<td>4.45 p=.49</td>
</tr>
</tbody>
</table>

**Table 8** Answers to the swallow-related QOL questions. Scores 0-3p. The lower score the better the function.

<table>
<thead>
<tr>
<th></th>
<th>Preoperative</th>
<th>6m Postoperative</th>
<th>12m Postoperative</th>
<th>Friedman test (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>0.0 (1.0)</td>
<td>0.5 (1.0)</td>
<td>0.5 (1.0)</td>
<td>0.67 p=.71</td>
</tr>
<tr>
<td>2.</td>
<td>0.0 (0.0)</td>
<td>0.0 (0.0)</td>
<td>0.0 (1.0)</td>
<td>2.00 p=.37</td>
</tr>
<tr>
<td>3.</td>
<td>0.0 (1.0)</td>
<td>0.0 (0.0)</td>
<td>0.0 (1.0)</td>
<td>2.67 p=.26</td>
</tr>
<tr>
<td>4.</td>
<td>0.0 (0.0)</td>
<td>0.0 (0.0)</td>
<td>0.0 (0.0)</td>
<td>4.00 p=.16</td>
</tr>
<tr>
<td>5.</td>
<td>0.0 (1.0)</td>
<td>0.0 (2.0)</td>
<td>0.0 (2.0)</td>
<td>5.00 p=.78</td>
</tr>
<tr>
<td>6.</td>
<td>0.5 (2.0)</td>
<td>1.0 (2.0)</td>
<td>0.5 (1.0)</td>
<td>2.55 p=.28</td>
</tr>
<tr>
<td>7.</td>
<td>1.0 (1.0)</td>
<td>1.0 (2.0)</td>
<td>0.5 (2.0)</td>
<td>0.74 p=.69</td>
</tr>
</tbody>
</table>

**Paper III - cZI DBS**

The findings from Paper III are visualized in Figure 6. Descriptive data on swallowing parameters are seen in Table 9, and UPDRS scores for secondary and non-motor features are summarized in Table 10. CZI DBS did not have an effect on the swallowing parameters penetration/aspiration, pharyngeal residue or preswallow spillage (p>.05). The median BMI score was increased with 1.1kg/m² at 12 months after cZI DBS surgery and the median increase in weight were +3.0kg after 12 months with cZI DBS. Figure 7 illustrates the distribution of patients in different BMI categories.
Swallowing parameters and Body mass index in cZI DBS - Paper III

Figure 6. Schematic graphical visualization of the findings in Paper III. Blue arrows illustrate non-significant numbers, green arrows represent a significant improvement and red arrows indicate significant worsening. Detailed descriptive data and statistical test-values are seen in Tables 9 and 10.

All reported secondary and non-motor features from the UPDRS part II were of slight or mild character. No cases of severe or moderate secondary symptoms were observed. There were difficulties with handling cutlery in 8 of 13 patients at baseline compared to 1 of 13 after 12 months with cZI DBS.
Preoperatively 9 of 13 patients reported slight or mild problems with speech compared to 13 of 13 patients after 12 months with cZI DBS.

**Table 9.** Medians, ranges and statistical tests for swallowing parameters

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>12m Postoperative</th>
<th>Friedman test (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test dose of L-dopa</td>
<td>Stim off</td>
<td>Stim on</td>
</tr>
<tr>
<td><strong>Liquid - Water</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penetration/aspiration</td>
<td>0.0 (4.0)</td>
<td>0.0 (4.0)</td>
<td>0.0 (2.0)</td>
</tr>
<tr>
<td>Pharyngeal residue</td>
<td>0.0 (1.0)</td>
<td>0.0 (1.0)</td>
<td>0.0 (1.0)</td>
</tr>
<tr>
<td>Preswallow spillage</td>
<td>1.0 (1.0)</td>
<td>1.0 (1.0)</td>
<td>1.0 (1.0)</td>
</tr>
<tr>
<td><strong>Solid - Biscuit</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penetration/aspiration</td>
<td>0.0 (2.0)</td>
<td>0.0 (2.0)</td>
<td>0.0 (5.0)</td>
</tr>
<tr>
<td>Pharyngeal residue</td>
<td>1.0 (1.0)</td>
<td>0.5 (1.0)</td>
<td>0.5 (1.0)</td>
</tr>
<tr>
<td>Preswallow spillage</td>
<td>1.0 (1.0)</td>
<td>0.5 (1.0)</td>
<td>1.0 (1.0)</td>
</tr>
<tr>
<td>Secretion Severity scale:</td>
<td>0.5 (2)</td>
<td>0.0 (3)</td>
<td>0.0 (3)</td>
</tr>
</tbody>
</table>

The lower the swallowing scores the better the function. *Significant according to Wilcoxon post-hoc test $z=-2.45, p=.01, r=-.48$. $r=z/\sqrt{(n_{preop}+n_{postop})}$. This table is a reproduction of a table in Paper III.

**Table 10.** Medians, ranges and statistical tests for BMI and UPDRS items

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>12m Postoperative</th>
<th>Wilcoxon test</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test dose of L-dopa</td>
<td>Stim on</td>
<td></td>
<td>z</td>
</tr>
<tr>
<td><strong>BMI (kg/m&lt;sup&gt;2&lt;/sup&gt;) (n=14)</strong></td>
<td>25.4 (20.0)</td>
<td>26.7 (18.5)</td>
<td>2.67</td>
<td>$p=.01$</td>
</tr>
<tr>
<td><strong>UPDRS (0-4p) (n=13)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cutting food</td>
<td>1.0 (2.0)</td>
<td>0.0 (1.0)</td>
<td></td>
<td>$-2.13$</td>
</tr>
<tr>
<td>Sialorrhea</td>
<td>0.0 (2.0)</td>
<td>1.0 (2.0)</td>
<td></td>
<td>1.41</td>
</tr>
<tr>
<td>Swallowing</td>
<td>1.0 (2.0)</td>
<td>2.0 (2.0)</td>
<td></td>
<td>.38</td>
</tr>
<tr>
<td>Speech</td>
<td>1.0 (2.0)</td>
<td>2.0 (1.0)</td>
<td></td>
<td>2.46</td>
</tr>
</tbody>
</table>

The lower the Unified Parkinson's Disease Rating Scale (UPDRS) scores the better the function. Body Mass Index (BMI) >25.0 is regarded as overweight. Figures marked in bold text show significant differences. $r=z/\sqrt{(n_{preop}+n_{postop})}$. This table is a reproduction of a table in Paper III.
Figure 7. Shift in distribution of Body Mass Index (BMI) 12 months after cZI DBS surgery. N=14. (Figure reproduced from Paper III)

**Paper IV- cZI DBS**

The results from Paper IV are summarized in Figure 8 and Figure 9. Descriptive data and significance testing are provided in Tables 11 and 12.

**Figure 8.** Schematic graphical visualization of the findings in Paper IV. Blue arrows illustrate non-significant numbers, green arrows represent a significant improvement and red arrows indicate significant worsening. Detailed descriptive data and statistical test-values are given in Table 11.
PD patients reported high scores on the SWAL-QOL questionnaire. Only one patient had a preoperative SWAL-QOL total score below 86p (cut-off score for clinically relevant dysphagia). Another patient had a SWAL-QOL score below 86p at 12 months after cZI DBS surgery. The SWAL-QOL total scores in the PD group were between 83 and 100p preoperatively and postoperatively between 82 and 100p.

In the postoperative analysis, four patients had improved SWAL-QOL total scores, three had worsened scores and two had unchanged scores. At group level, there were no significant changes between preoperative and postoperative ratings on the SWAL-QOL questionnaire (all p>.05, r=.00-.27).

The preoperative median VA-scale score was 94% (range 59-100) while the 12 months postoperative VA-scale score was 98% (range 59-100). This difference was not significant (z=.388, p>.05, r=.09).
Table 11. Descriptive data. Wilcoxon signed-rank test for comparison between baseline and 12 months after cZI DBS surgery

<table>
<thead>
<tr>
<th>SWAL-QOL</th>
<th>PD group (n=9)</th>
<th>Wilcoxon signed-rank test and effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before cZI DBS</td>
<td>12m after cZI DBS</td>
</tr>
<tr>
<td></td>
<td>median (range)</td>
<td>median (range)</td>
</tr>
<tr>
<td>Food selection</td>
<td>100 (100-100)</td>
<td>100 (88-100)</td>
</tr>
<tr>
<td>Burden</td>
<td>100a (63-100)</td>
<td>88 (63-100)</td>
</tr>
<tr>
<td>Mental health</td>
<td>100 (70-100)</td>
<td>100 (85-100)</td>
</tr>
<tr>
<td>Social functioning</td>
<td>100 (100-100)</td>
<td>100 (100-100)</td>
</tr>
<tr>
<td>Fear of eating</td>
<td>100 (69-100)</td>
<td>97 (75-100)</td>
</tr>
<tr>
<td>Eating duration</td>
<td>75 (50-100)</td>
<td>88 (38-100)</td>
</tr>
<tr>
<td>Eating desire</td>
<td>92 (67-100)</td>
<td>100 (58-100)</td>
</tr>
<tr>
<td>Communication</td>
<td>88 (75-100)</td>
<td>100a (50-100)</td>
</tr>
<tr>
<td>Sleep</td>
<td>88 (38-100)</td>
<td>88 (63-100)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>75 (42-100)</td>
<td>75 (50-100)</td>
</tr>
<tr>
<td>Symptom scale</td>
<td>91 (68-100)</td>
<td>82 (66-100)</td>
</tr>
<tr>
<td>SWAL-QOL total</td>
<td>94 (83-100)</td>
<td>95 (82-100)</td>
</tr>
</tbody>
</table>

SWAL-QOL: Swallowing Quality of Life. PD: Parkinson’s Disease. cZI DBS: caudal Zona Incerta Deep Brain Stimulation. The higher the score the better the function. Estimated effect size: $r = z / \sqrt{(n_{\text{patients}} + n_{\text{controls}})}$. aItem missing from one patient. bSign rank test was used due to skewness.

Table 12. Descriptive data. Wilcoxon signed-rank test for differences between the PD group with cZI DBS and controls

<table>
<thead>
<tr>
<th>SWAL-QOL</th>
<th>PD group 12m after cZI DBS</th>
<th>Controls (n=9)</th>
<th>Wilcoxon signed-rank test and effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>median (range)</td>
<td>median (range)</td>
<td>z</td>
</tr>
<tr>
<td>Food selection</td>
<td>100 (88-100)</td>
<td>100 (100-100)</td>
<td>-0.707b</td>
</tr>
<tr>
<td>Burden</td>
<td>88 (63-100)</td>
<td>100 (100-100)</td>
<td>-2.23</td>
</tr>
<tr>
<td>Mental health</td>
<td>100 (85-100)</td>
<td>100 (95-100)</td>
<td>0.000b</td>
</tr>
<tr>
<td>Social functioning</td>
<td>100 (100-100)</td>
<td>100 (100-100)</td>
<td>0.000</td>
</tr>
<tr>
<td>Fear of eating</td>
<td>97 (75-100)</td>
<td>100 (75-100)</td>
<td>-0.756</td>
</tr>
<tr>
<td>Eating duration</td>
<td>88 (38-100)</td>
<td>100 (63-100)</td>
<td>-1.37</td>
</tr>
<tr>
<td>Eating desire</td>
<td>100 (58-100)</td>
<td>100 (83-100)</td>
<td>0.000b</td>
</tr>
<tr>
<td>Communication</td>
<td>100a (50-100)</td>
<td>100 (100-100)</td>
<td>-0.707b</td>
</tr>
<tr>
<td>Sleep</td>
<td>88 (63-100)</td>
<td>63 (50-100)</td>
<td>1.62</td>
</tr>
<tr>
<td>Fatigue</td>
<td>75 (50-100)</td>
<td>67 (50-100)</td>
<td>-3.58</td>
</tr>
<tr>
<td>Symptom scale</td>
<td>82 (66-100)</td>
<td>98 (86-100)</td>
<td>-2.38</td>
</tr>
<tr>
<td>SWAL-QOL total</td>
<td>95 (82-100)</td>
<td>100 (93-100)</td>
<td>-1.76</td>
</tr>
</tbody>
</table>

SWAL-QOL: Swallowing Quality of Life. PD: Parkinson’s Disease. cZI DBS: caudal Zona Incerta Deep Brain Stimulation. The higher the score the better the function. Estimated effect size: $r = z / \sqrt{(n_{\text{patients}} + n_{\text{controls}})}$. aItem missing from one patient. bSign rank test was used due to skewness. *significant difference, $p<.05$. 

27
**PD group vs. Control group**

The PD group reported significantly lower scores in the ‘burden’ subscale and in the ‘symptom’ scale compared to the controls. The difference in medians between the PD group and the controls regarding SWAL-QOL scores did not reach statistical significance ($p=.08$, $r=-.42$). Other SWAL-QOL subscale items that showed non-significant differences but had effect sizes above .30, were ‘sleep’ and ‘eating duration’ ($p=.11$, $r=.38$ and $p=.17$, $r=-.32$).

**Intra-rater and inter-rater reliability**

In Paper I the inter-, and intra-rater reliability was 95%. Paper II had 95% intra-rater reliability and Kappa scores for intra-rater reliability and inter-rater reliability were .88 and .72. In Paper III, the Spearman’s rho was used to test intra-rater and inter-rater agreements for penetration-aspiration, preswallow spillage, pharyngeal residue and secretion severity scale. Intra-rater agreements showed high correlations (Sample from Paper II: $r_{s}=.85$, $r_{s}=.81$, $r_{s}=.93$, and $r_{s}=1.00$, $p<.01$. New sample added in Paper III: $r_{s}=.89$, $r_{s}=.94$, $r_{s}=.79$, and $r_{s}=1.00$, $p<.01$). Test of inter-rater agreements showed moderate correlations ($r_{s}=.68$, $r_{s}=.84$, $r_{s}=.57$, and $r_{s}=.63$, $p<.01$).
Discussion

The purpose of this thesis was to improve the understanding of the effect of STN and cZI DBS on pharyngeal swallowing function, swallow-specific QOL and swallowing related non-motor and secondary symptoms in patients with PD.

The first specific research aim was to elucidate whether STN and cZI DBS have an effect on pharyngeal swallowing parameters. The results from Papers I-III conclude that the patients selected to STN and cZI DBS had good preoperative swallowing function and that neither STN nor cZI DBS had a negative effect on the swallowing function.

The second specific research aim was to examine whether STN and cZI DBS have an effect on self-estimated swallowing function. The results from Paper I concluded that patients with STN DBS rated their swallowing as improved with STN DBS turned on compared to when STN DBS was turned off. The postoperative scores with STN DBS turned on were, however, equal to the preoperative ratings with L-dopa. The results from Paper II and IV indicated that the PD patients with cZI DBS rated their swallowing as equally good preoperatively and postoperatively as well as with and without cZI DBS turned on.

The third specific research aim concerned the effect of cZI DBS on secondary and non-motor features. In Paper III, cZI DBS was found to cause an increased body weight 12 months after the surgery. Also mild speech problems increased after 12 months with cZI DBS. Handling of cutlery was clearly improved 12 months after cZI surgery.

The last specific research aim concerned the effect of cZI on swallow-specific QOL. The results from Paper IV indicated that the PD patients rated their swallow-specific QOL as being equally good before DBS surgery and 12 months after cZI DBS. The results also indicated that patients with cZI DBS rated their swallow-specific QOL close to ratings by controls of the same age.

The results of the thesis are encouraging for clinicians and support the notion that neither swallowing function nor self-reported swallow-specific QOL are negatively affected by STN or cZI DBS. This is also in line with the previous work by Ciucci et al., Lengerer et al., and Silbergleit et al.,99-100. The studies by Ciucci et al. and Silbergleit et al. report small improvements due to STN DBS when patients are tested in the off L-dopa medication condition, while in our study (Paper I) all postoperative examinations were performed.
with L-dopa medication. This may explain why no significant improvements could be found in our study, as L-dopa medication could mask possible improvements by the DBS. However, it could be argued that such small scale improvements, manifested only in a medication off state, are of limited practical clinical value.

The results from the present reports indicate good preoperative swallowing function in patients with STN DBS and cZI DBS. Similar preoperative scenarios, in which patients show satisfactory swallowing function, are also described in the studies by Ciucci et al., Lengerer et al. and Troche et al. While Ciucci et al. and Lengerer et al. report no negative effects of STN DBS, Troche et al. found increasing penetration and aspiration postoperatively, presumably due to the STN DBS. It should be noted that all patients in the study of Troche et al. had unilateral DBS, while four of eight patients in our STN DBS study had bilateral DBS. The reports by Lengerer et al. and Silbergleit et al. included patients with bilateral DBS, while Ciucci et al. did not state whether the included patients had uni- or bilateral STN DBS. It is quite possible that unilateral DBS might affect swallowing function differently from bilateral stimulation, but to date there are not enough research data to allow any conclusions regarding this proposition.

It is important to note that Troche et al. report worsened penetration and aspiration scores postoperatively compared to preoperative baseline values. No postoperative comparison between stimulation on and stimulation off scores was performed. This makes it impossible to address the causes of swallowing deterioration since the STN DBS surgery itself, the DBS stimulation or the natural progression of the disease, may each individually or together cause swallowing deterioration.

It has been reported that swallowing function can be preserved in early stages of PD, and that the estimated onset of swallowing problems can be up to 10.8 years (130 months). When interpreting the results of this thesis, it should be kept in mind that the disease durations were shorter than reported in several other published studies, and also that the initial swallowing problems were mild. The median disease durations in the present group of patients were between 6 and 10 years (individual durations ranged between 2 and 13 years). The mean disease duration in the Troche et al. study and the Lengerer et al. study was 11 years. Ciucci et al. and Silbergleit et al. did not report disease duration. The outcome of this thesis can thus not be generalized to patients with severe dysphagia or with longer disease durations.
**Effect of DBS on self-estimated swallowing function**

In the STN DBS study (Paper I), as well as in the study by Silbergleit et al., the patients reported an improved self-perceived swallowing function postoperatively compared to baseline\(^{100}\), despite the fact that the instrumental examinations with FEES and VFSS did not show any significant improvements. Discrepancies between subjective and instrumental swallowing measures have previously been reported\(^{27–31,113}\). In these reports, patients underestimate their swallowing problems compared to instrumental evaluations. In this thesis, patients with STN DBS report a positive effect of treatment, contrary to the instrumental measures, which do not. In accordance with the suggestions by Silbergleit et al. \(^{100}\), possible explanations for this discrepancy can be suggested. One reason for the patients’ self-perceived improvement may be that the ameliorated overall motor function due to STN DBS also causes an improved self-perception of swallowing function. Moreover, an inclination by the patient to provide a desirable outcome to the research team, or a conventional placebo effect might explain the discrepancy\(^{100}\). It is also possible that the patients experience subtle positive effects of the STN DBS that are not possible to confirm with a FEES examination, but may be evident to the patients in their daily lives. To detect such subtle changes, the use of a self-report tool like SWAL-QOL would have been preferable. Unfortunately, no Swedish version of the SWAL-QOL was available at the initiation of the study reported in Paper I.

With regard to cZI DBS, the treatment did not change the patients’ self-perceived swallowing function, as assessed by the VA-scale or the short QOL-questions. These results were well in accordance with the instrumental measures from the FEES.

**Effect of cZI DBS on swallowing related secondary and non-motor features**

Weight gain after STN DBS has previously been reported and the results in Paper III indicate similar weight changes after cZI DBS\(^{95–97}\). The proportion of weight gain and the increase in BMI is similar to, or lower than what has been reported from groups with STN DBS\(^{97}\). The findings reported in Paper III are the only data available regarding patients’ weight after DBS in cZI.

At baseline, approximately 50% of the patients in the cZI DBS group experienced slight or mild problems with sialorrhea and swallowing as measured by UPDRS-II. This proportion was not significantly increased after cZI DBS.
The ability to cut food and handle cutlery was improved with cZI DBS. Preoperatively, 8 of 13 patients reported slight or mild problems with handling cutlery compared to 1 of 13 patients after 12 months with cZI DBS.

Problems with speech is a common adverse effect after DBS, but also an expected sign as the disease progresses along its natural course, making studies of speech in relation to DBS difficult and complex. In this group, cZI DBS seems to have a small negative impact on speech. At the 12 months follow up, all cZI DBS patients reported speech deterioration according to the UPDRS-II. However, it should be noted that the observed speech problems were of slight or mild character, and that UPDRS in such a situation is not an optimal tool for evaluation of speech. However, a parallel study by Johansson et al.94, based on partly the same group of patients, also concluded that cZI DBS had a negative effect on speech intelligibility.

**Effect of cZI DBS on swallow-specific QOL**

The fourth study in this thesis (Paper IV) is the first prospective and longitudinal study on self-reported swallow-specific QOL in PD patients selected for cZI DBS. The study was conducted to broaden the perspective regarding cZI DBS and swallowing, and moreover to extend and expand the outcomes of Paper II and Paper III. The use of swallowing QOL questionnaires emphasizes the move toward patient centred care, which highlights the individual’s particular health care needs and empowers patients to become active participants in their own care.

The cZI DBS patients in Paper IV rated their swallow-specific QOL as equally good before and after cZI DBS. This was true for the SWAL-QOL total score as well as for all the subscales. Both pre- and postoperatively, the SWAL-QOL scores were high compared to PD populations in general49,51, but similar to the scores from early-stage PD patients50.

Preoperatively, only one patient reported a SWAL-QOL total score below 86p which is the cut-off score for clinically significant dysphagia110. Postoperatively, this patient had a SWAL-QOL total score above cut-off, while another patient reported a SWAL-QOL total score below cut-off. The outcomes from Paper IV indicate that cZI DBS treatment does not have a clinically significant negative impact on swallow-specific QOL.

It is well known that PD patients often underestimate their swallowing problems and this may have affected the outcome of Paper IV26,29. However, since there is consensus between the three papers on cZI DBS, it is unlikely that the patients have underestimated their swallowing problems in this
context. This is the first report on self-reported swallow-specific QOL in patients with cZI DBS and the results in Paper IV are also in congruence with the findings of the instrumental examinations in Papers II and III.

**Swallow-specific QOL in patients with cZI DBS vs. controls**

The postoperative scores from the PD patients with cZI DBS were compared to scores from nine gender matched controls of comparable age and marital status. The control group reported a SWAL-QOL total score of 100p while the PD patients reported a score of 95p. This can be interpreted as PD patients and controls having the same level of swallow-specific QOL as this difference was not significant. Even so, the PD patients had significantly lower scores on the ‘symptom’ scale and the ‘burden’ scale. This indicates that the PD patients experienced more swallowing symptoms and suffered more from the swallowing problems than the controls, although they did not experience an overall decrease in swallow-specific QOL. The relatively short disease durations and specific inclusion criteria in our study might be the explanation for this outcome. Earlier studies comparing SWAL-QOL between PD patients in general and controls have reported a significant decrease in swallow-specific QOL in PD patients.

**Strengths and limitations of the studies**

The study design with examinations pre- and postoperatively at fixed time points, with as well as without DBS stimulation is a major strength of this thesis. In addition, all swallowing examinations were done according to the same protocol and by the same examiner. Such a study design enables a comparison of pre- and postoperative swallowing function as well as comparisons with and without DBS postoperatively. A similar study design was also used by Silbergleit et al. The study protocol adopted by Troche et al., including retrospective data from preoperative examinations and postoperative examinations with stimulation turned on, prevents an analysis of a specific effect of the DBS on swallowing function. Ciucci et al. only reported postoperative scores, while Lengerer et al. retrospectively reported pre- and postoperative scores, but at variable time points in relation to the DBS surgery, making the outcome difficult to interpret in relation to our design.

This thesis broadens the picture of swallowing function in patients with DBS, as both instrumental examinations with validated rating scales and self-report scales were used. Blinded and randomized ratings were performed as well as calculations of intra- and interrater reliability. Taken together, this provides a robust body of knowledge regarding the topic.
The low number of participants included in the studies, caused by the restricted number of available patients, is the main limitation in this thesis. Our material is based on available PD patients in the northern region of Sweden suitable for STN DBS or cZI DBS surgery. The small sample size affects the power negatively and increases the risk of type II errors. Bonferroni corrections were not included in the analyses, as this would have further increased the risk of type II errors\textsuperscript{114}. When examining possible negative effects of a treatment it is crucial to be aware of the risks of low power. If the power is low, there is the risk of falsely concluding that a treatment is safe, even though there are negative effects that can not be observed due to low power\textsuperscript{115}. Thus, in Papers III and IV both significance testing and assessments of estimated effect sizes were used to enable detection of non-significant differences with moderate effect sizes.

The gender distribution was uneven, which has to be taken into consideration when interpreting the results. It has been reported previously that females are under-represented among patients treated with DBS\textsuperscript{116}. Hamberg and Hariz performed interviews with men and women regarding their decision making process before DBS surgery\textsuperscript{117}. Their results showed that the men more often ‘took their own initiative’ regarding DBS or ‘agreed when offered DBS’, while a ‘hesitating and waiting’ approach was more common among the women in the study\textsuperscript{117}. These outcomes may also explain the gender biases we noted in our study.

The postoperative examinations were all done with L-dopa medication. This limits the study design since the effect of DBS cannot be isolated from the impact of medication. The decision to maintain medication during postoperative examinations was made on ethical grounds, as the patients underwent a range of different tests and it was important to minimize the number of tests off medication and the medical discomfort caused by withdrawal of medication and stimulation.

**Future research and clinical implications**

As the main limitation of the thesis is the low number of patients it is important to perform larger studies regarding STN and cZI DBS and swallowing. Larger studies including both instrumental examinations and self-report scales are needed. The study design must enable longitudinal comparison between pre- and postoperative time points as well as changes between stimulation off and stimulation on. In the future, it will also be important to investigate the effect of different stimulation parameters in order to optimize the effect on swallowing function. Also, the question
regarding the effect of unilateral versus bilateral DBS on swallowing needs to be addressed in future studies.

The results in Paper III showed that cZI DBS resulted in a weight gain similar to that seen for STN DBS. Due to this, cZI patients need to be informed about this preoperatively and be given help to manage their possible weight gain. The reasons for weight gain after DBS is not clear and must be investigated further.

The timespan of the studies in this thesis is from baseline to 12 months after DBS surgery. There are to date no studies that follow the swallowing function of DBS patients over a longer timespan (>12 months). Future research could benefit from following patients over time and this would preferably be executed as a cohort-matched control study to control for disease progression.

As the cZI studies in this thesis are so far the only studies examining cZI DBS and swallowing function, they contribute with important clinical information. Patients with mild swallowing problems seem to be able to undergo STN DBS or cZI DBS without increasing the risk of pharyngeal swallowing problems.
Conclusions

DBS in STN or cZI did not have a negative effect on swallowing function or swallow-specific QOL in this cohort. Patients with STN DBS reported a self-perceived improvement in swallowing function when DBS was turned on. Patients with cZI DBS had an overall good swallow-specific QOL throughout the conduct of the study and their swallow-specific QOL was not negatively affected by cZI DBS. There seems to be no increased risk for aspiration or penetration due to surgery or stimulation for either the STN DBS or cZI DBS groups. CZI DBS caused weight gain postoperatively. Since the sample sizes in these cohorts are small, the findings need to be interpreted with caution and confirmed in larger studies.
Acknowledgements

I would like to thank everyone who supported me during the work with this thesis and the papers. I would especially like to thank the following persons:

Katarina Olofsson, my patient and admirable supervisor, for generously supporting me in my work and always being ready to have an open discussion.

Jan Linder and Erik Nordh, co-supervisors, for support, strategic tips and review of the manuscripts.

Linda Kulneff, Patric Blomstedt, Caterina Finizia, Johanna Hedström, Jan van Doorn, Lina Holmén and Elin Rova for collaboration and co-authoring.

Anna Fredricks and Anders Asplund for management of patients, administrative and technical support.

Jan van Doorn for revision of the text.

All participants in the studies without whom the studies would have been nothing.

Helena and Hans-Erik Jansson, for maintaining a superb and flexible support service including taking care of Nils, lunches, tea breaks, computers etc.

Christoffer, my husband, for supporting me and believing in what I do.
Funding

This work was supported by:

- The Arvid and Greta Olin Foundation (The Swedish Cultural Foundation in Finland)
- The Swedish Parkinson’s Foundation
- Svensk-Österbottniska Samfundet r.f.
- Umeå University
- Norrbotten County Council
- Västerbotten County Council
References


2. Parkinson, J. *An essay on the shaking palsy*. (Printed by Whittingham and Rowland for Sherwood, Neely, and Jones, 1817).


