Swallowing and Deep Brain Stimulation
Swallowing function in Parkinson’s disease after subthalamic nucleus and caudal zona incerta Deep Brain Stimulation

Stina Sundstedt
Dedicated to all who contribute to new knowledge by taking part in medical research
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Abstract

**Background** Swallowing problems are common in Parkinson’s disease, and these affect morbidity and mortality largely due to aspiration-induced pneumonia. Even mild dysphagia affects patient Quality of Life. Deep Brain Stimulation (DBS), a surgical treatment for Parkinson’s disease, improves overall motor function, though the effect of DBS on swallowing function is not clear. The aim of the studies in this thesis was to improve our understanding of the effect from DBS of caudal zona incerta and subthalamic nucleus on pharyngeal swallowing function. Specific aims were to compare DBS effects over time postoperatively (6 & 12 months) for swallowing function, on and off stimulation, with a preoperative baseline assessment in order to identify possible negative swallowing effects of DBS.

**Methods** Eight patients with DBS in caudal zona incerta and eleven patients with DBS in subthalamic nucleus were included in the two studies. The effect of DBS on swallowing function was evaluated by self-estimation on a visual analogue scale and fiberoptic endoscopic evaluation of swallowing function with a predefined swallowing protocol including Rosenbek’s Penetration/Aspiration Scale, Secretion Severity Scale, preswallow spillage, pharyngeal residue and pharyngeal clearance. The patients with caudal zona incerta DBS also answered questions regarding swallowing-related Quality of Life. All patients received L-dopa treatment during postoperative assessments.

**Results** There was no clear effect of DBS on swallowing function in the two samples. The occurrence of aspiration, secretions, pharyngeal residue or clearance was not affected by the surgery or the stimulation. In the subthalamic nucleus DBS sample, self-estimations revealed an improvement with stimulation turned on. For the caudal zona incerta DBS patients, no effect of DBS was seen on the results from the swallowing-related QOL questions.

**Conclusion** Subthalamic nucleus DBS and caudal zona incerta DBS did not appear to have a negative effect on swallowing function in this cohort. Patients with subthalamic nucleus DBS reported a self-perceived improvement in swallowing function after DBS. There appears to be no increased risk for aspiration or penetration due to surgery or stimulation regardless of stimulation site. 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
QOL  Quality of Life
CI  confidence interval
SWAL-QOL  Swallowing Quality of Life Questionnaire
L-Dopa  levodopa
DBS  Deep Brain Stimulation
STN  subthalamic nucleus
cZI  caudal zona incerta
FEES  fiberoptic endoscopic evaluation of swallowing function
%DSF  percentage deterioration of swallowing function
CAPSIT-PD  Core assessment program for surgical interventional therapies in Parkinson’s disease
UPDRS  Unified Parkinson’s Disease Rating Scale
P/A  Penetration/Aspiration scale
PS  preswallow spillage
Phr  pharyngeal residue
CC  pharyngeal clearance
SS  secretion scale
C1  consistency 1: water
C2  consistency 2: 50 ml water and 5 ml jellification powder
C3  consistency 3: 50 ml water and 10 ml jellification powder
C4  consistency 4: 50 ml water and 15 ml jellification powder
C5  consistency 5: a biscuit with a smear of C1 on top.
Preface

The thesis is based on an introduction and the following papers:


The articles are referred to in the text by using their Roman numerals. Permission from Acta Neurologica Scandinavica to reprint Paper I and Paper II has been given by Wiley & Sons according to the copyright transfer agreement.
Sammanfattning på svenska

Parkinsons sjukdom är en progressiv neurologisk sjukdom som kännetecknas av motoriska problem. Årligen insjuknar 115 personer per 100 000 invånare i Sverige. Typiska symptomen är skakningar i händer och armar, stelhet i musklerna, förlängsamt rörelser och nedsatt kroppssstabilitet. Förutom dessa symptom förekommer ofta påverkan på tal- och sväljningsfunktionen.

Den normala sväljningen kan delas in i fyra olika faser. Denna licentiatavhandling har huvudsakligen studerat sväljningsproblem i svalget, till skillnad från sväljningssvårigheter som kan uppstå i matstrupen eller munhålan. Exempel på sväljningssvårigheter i svalget är då mat ligger kvar efter sväljningen eller sväljs ner i luftstrupen samt svårigheter med att initiera sväljningen. Det är vanligt med sväljningssvårigheter hos äldre personer och felsvälvning ner i lungorna kan orsaka både sjuklighet och dödlighet.

Cirka fyra av fem Parkinsonpatienter får sväljningssvårigheter under sjukdomsförloppet. I början av sjukdomsförloppet vid Parkinsons sjukdom är sväljningsproblemen vanligen lindriga men även lindriga sväljnings-svårigheter kan ge konsekvenser för patienterna och deras anhöriga.


Studierna inkluderade åtta patienter med djuphjärnstimulering i kaudala zona incerta och elva patienter med djup hjärnstimulering i

Resultatet visade att sväljningen inte påverkades negativt av djup hjärnstimulering hos de patienter som deltog i studien. Gruppen som fått djup hjärnstimulering i subthalamuskärnan skattade sin sväljning som bättre med stimulering jämfört med utan stimulering. Endast lindriga till måttliga sväljningssvårigheter upptäcktes bland patienterna.

Medianen för sjukdomstiden för patienterna i de två studierna var 6,5 år. Den relativt korta sjukdomstiden kan ha bidragit till att sväljningssvårigheterna var lindriga. Det är viktigt att göra större studier med patienter som varit Parkinsonsjuka under en längre tid för att kunna dra säkra slutsatser. De två studierna som ingår i denna licentiatavhandling ger en fingervisning om att djup hjärnstimulering inte ökar sväljningsproblemen bland Parkinsons patienter med lindriga sväljningsproblem. Studieresultaten ger oss viktig information att delge patienterna som ska genomgå djup hjärnstimulering.
Background

*Parkinson’s disease*

James Parkinson was the first to describe and categorize the illness that is now recognized as Parkinson’s disease (PD). In 1817 he wrote his widely read essay named “An essay on the shaking palsy”. Today, it is recognized that PD is one of the most common neurodegenerative diseases in Europe, with a prevalence rate in Sweden of 115/100,0003. The peak incidence of PD occurs at 70 to 79 years, and the reported mean ages of symptom onset are between 60 and 72 years4. Symptom onset seems to be earlier in males and, although some studies found equal prevalence rates for men and women5,6, others have presented a larger proportion of males affected by the disease3,4.

The etiology of the disease is still unclear. Among risk factors for PD are exposure to pesticides, advancing age, and family history of PD7–9. Degeneration of neurons in the substantia nigra and the loss of the neurotransmitter dopamine due to degeneration play a role in the origin of the cardinal symptoms8,9, which are tremor at rest, rigidity (muscles’ resistance to passive movement), bradykinesia (slowing down of spontaneous and automatic movements) and postural instability9,10. The motor-symptoms are often unilateral, with one side of the body more affected in the early course of the disease. As the disease progresses, the symptoms can become bilateral though an asymmetry of motor symptoms often remains over the course of the disease10.

In addition to the cardinal symptoms associated with PD, non-motor and secondary motor symptoms are often seen. Neuropsychiatric non-motor symptoms include apathy, anxiety, depression, dementia, and psychosis11,14. Autonomic nervous system dysfunction can be manifest as hypertension, constipation, or sleeping disorders14. Secondary motor symptoms, such as dysarthria, hypophonia, dystonia, sialorrhea, and dysphagia, can negatively influence the lifestyle of patients11,13.

When assessing the well-being of individuals, as well as the impact of diseases and symptoms on patients’ lives, the term Quality of Life (QOL) is sometimes used. Measurement of QOL is performed using rating scales for aspects of daily life and activities, and these can be analyzed in relation to other aspects of a disease. For patients with PD, depression is one of the symptoms that most affects QOL15. Disability, postural instability, cognitive impairment, as well as undesirable side-effects of PD medications are other factors which can contribute to low QOL16. Female gender is associated with
lower QOL scores for PD patients in some studies. Secondary motor symptoms, such as dysphagia, are likely to have social and psychological consequences in PD patients, and dysphagia has a negative effect on QOL in elderly populations in general.

**Swallowing and dysphagia**

Dysphagia is defined as eating and swallowing difficulties. *Dys* means bad and *phagos* to eat. In elderly people living at home, the prevalence of dysphagia is between 11% and 14%.

The act of swallowing can be divided into four phases. The pre-oral phase includes patient ability to sit and eat, state of hunger, and the milieu of the meal. Swallowing difficulties in this phase include problems bringing food to the mouth and negative milieu factors, such as anxiety.

In the oral phase, which is largely under voluntary control, food already in the mouth is blended with saliva and processed by the teeth. The posterior part of the tongue meets the soft palate to prevent premature spillage. The swallowing reflex is elicited when the processed bolus passes the area of the pharyngeal pillars. Swallowing problems that may occur in the oral phase include lingual tremor, repetitive tongue rolling, poor bolus formation, delayed oral transit, premature spill of bolus, and leakage through lips.

The pharyngeal phase, where the bolus is transported from the oropharynx into the esophagus, starts with the swallowing reflex. The soft palate is elevated to prevent leakage to the nasopharynx. The glottis is closed as the true and false vocal cords are adducted, and the hyoid bone and the larynx are elevated to prevent aspiration. The pharyngeal phase of the swallowing is normally about 0.7 seconds long. Pharyngeal swallowing problems include aspiration (bolus passing below the vocal cords), penetration above the vocal cords, prolonged movements of the pharyngeal muscles, problems initiating swallowing, and residual of food in the valleculae or piriform sinus.

Aspiration of food and liquids can lead to pneumonia, and therefore aspiration is an important dysphagia symptom. Residual food bolus in the valleculae and sinus piriformes can cause secondary aspiration.

In the esophageal phase, which is the last phase, the bolus is transported from the upper esophageal sphincter, through the esophagus, and into the stomach. This transition of bolus takes approximately 5.9 seconds. Swallowing problems include prolonged transition through the esophagus,
stasis of the bolus, and gastro-esophageal reflux. Esophageal swallowing problems are not further discussed in this thesis.

When examining swallowing in these phases, different clinical methods are employed, including video fluoroscopy and fiberoptic endoscopic examination of swallowing function (FEES). A range of subjective self-assessment scales and interviews are also used to assess dysphagia.

A discrepancy between objective measures of swallowing problems and subjective ratings of dysphagia are often observed in patients with swallowing difficulties. Objective measures often give higher prevalence of swallowing problems than self-assessments. Some of the discrepancy might be explained by the different types of questions asked to the patients. Parker et al. found that although some patients were aware of having dysphagic symptoms, they did not perceive themselves as having a ‘swallowing problem’. As prevalence differs depending on which methods are used to identify swallowing problems, it is important to include examinations of the swallowing function together with self-assessments when studying swallowing in different patient populations.

**Swallowing problems in patients with Parkinson’s disease**

Oropharyngeal swallowing problems and dysphagia are common among patients with PD. Swallowing difficulties increase mortality risk in PD patients, and aspiration pneumonia is the comorbidity with the highest mortality rate for PD patients in long term care.

When swallowing is examined with video fluoroscopy or FEES, the prevalence of swallowing problems is 82%±5%, 95% confidence interval (CI95). The prevalence of self-perceived dysphagia in community living patients with PD is 35±6% (CI95). According to Kalf’s meta-analysis, four out of five patients with PD show abnormal swallowing function.

Volonte et al. reported abnormalities in the oral phase of swallowing in 70% of the patients, assessed using a modified dysphagia rating scale. The abnormalities included hypokinetic changes for lingual protrusion and palatal elevation. Other swallowing changes related to PD include problems with initiation of swallowing, prolongation of the movements of the larynx and the oral-pharyngeal transit time, as well as decreased suction pressure.

Patients with PD have more post-swallow pooling in the valleculae and sinus piriformes, along with silent saliva aspiration, compared to healthy
However, in early stage PD, swallowing function has been shown to be no different than swallowing function in healthy controls\textsuperscript{48}.

Associations between swallowing difficulties, severity of disease, and disease duration has been examined in several studies, and there is some variation in results\textsuperscript{38,40,49,50}. Some studies present significant associations between these parameters\textsuperscript{40, 49} while others do not\textsuperscript{38,46,50}. The specific details for swallowing parameters and measures of disease severity differ between the studies, which probably contribute to the disparate results. The association seems to be stronger between disease severity and dysphagia than between dysphagia and disease duration.

The impact of swallowing problems on QOL is an important aspect of PD, which has received recent attention\textsuperscript{51}. Validated questionnaires like Swallowing Quality of Life (SWAL-QOL) have been used to examine swallowing related QOL in PD patients, and lower scores on swallowing QOL parameters compared to age-matched controls have been reported\textsuperscript{51,52}.

Semi-structured interviews were conducted by Miller et al. to investigate QOL in PD\textsuperscript{53}. The interviews identified factors including long eating durations, fear of choking, food selection, feelings of guilt, and concerns about the extra burden on the caregivers. The conclusion from the study was that even mild swallowing problems have a negative impact on the patients and their caregivers. As swallowing problems affect QOL and increase mortality risk, it is important to consider swallowing problems when choosing treatments for PD.

\textit{Levodopa and swallowing function}

The most common treatment alternative for PD patients is levodopa medication (L-Dopa)\textsuperscript{54}. Hornykiewicz was the first to perform trials with L-Dopa for patients with PD in 1961, and since then it has been used in the treatment of general motor symptoms in PD patients\textsuperscript{54}.

The effect of L-Dopa on secondary and non-motor functions is not well known\textsuperscript{55-59}, and the possible effects of L-dopa treatment on swallowing function have been identified but not confirmed\textsuperscript{31}. Some studies have reported small improvements in both the pharyngeal and oral phase of swallowing\textsuperscript{42,31}, while others suggest that oral swallowing time may be prolonged and lung function impaired due to L-dopa\textsuperscript{31,57}. Risk for aspiration does not seem to be increased\textsuperscript{31,57}. 

\textsuperscript{4}
Monte et al. compared swallowing function in dyskinetic and non-dyskinetic patients, and found that a higher dose of L-Dopa brought about higher oropharyngeal swallow efficiency⁵⁸. A systematic review by Menezes et al., examining the effect of L-dopa on swallowing function, suggested that there was no strong evidence for systematic improvements due to treatment with L-Dopa⁵⁹.

**Stereotactic surgery for Parkinson’s disease**

Stereotactic surgical procedures as treatment for PD were introduced in 1950s⁵⁶. At that time, there were no pharmaceutical therapies available for PD, and stereotactic ablative surgery emerged as a treatment alternative for PD and other movement disorders⁶⁰. The risks and complications associated with the surgical procedures limited their popularity, and when L-Dopa treatment was introduced, the use of surgical treatments decreased for many years⁵⁶,⁶¹.

The use of stereotactic surgery as a treatment of movement disorders increased again during the 1990s. At that point in time, there was a greater understanding of mechanisms of PD as well as complications related to L-Dopa⁶⁶. The surgical and imaging techniques had by that time also improved considerably⁶⁶. Chronic electric stimulation of the brain, which had earlier been used in the treatment of chronic pain and behavioral disorders, was now recognized to improve motor function in PD⁶².

Pollak, Benabd, and colleagues were among the first to perform Deep Brain Stimulation (DBS) in the subthalamic nucleus (STN)⁶³–⁶⁵. The DBS surgery is performed with a stereotactic extra-cranial frame and imaging techniques. Electrodes are implanted bilaterally into the STN during local anaesthesia using carefully planned trajectories to reach the center of the STN (Figure 1)⁶⁵. Detailed radiographic assessment is used to ensure that the electrodes are in the right location. Extension leads are connected to a programmable electric pulse generator which is placed under the skin in the patient’s subclavicular region. Postoperatively, the stimulator settings are carefully tested and adjusted⁶⁵.

Positive effects on rigidity, tremor, akinesia and gait are usually obvious very quickly. In this way, STN DBS has developed into an established treatment alternative in PD. One benefit of modern DBS, compared to the lesion techniques used in the 1950s, is that DBS is reversible and the stimulation can be turned off, or the electrodes can be removed if complications arise⁶⁶.
There is still no widespread agreement regarding the mechanisms behind the effect of DBS. It has been hypothesised that stimulation affects the target nucleus as well as the surrounding fiber pathways. As a result, DBS creates a complex pattern of excitatory as well as inhibitory effects. This complex pattern may have an effect on the basal ganglia thalamocortical network in general.

Ever since the first DBS operations, the surgical techniques and the medical hardware have been refined, and the stimulation targets as well as the medical indications for surgery have expanded. It has been estimated that over 25,000 DBS operations have been performed around the world to date.

The efficacy of DBS on motor symptoms and improvements in health related QOL in PD patients have been documented. There is clear evidence that STN DBS improves UPDRS motor scores and the scores for activities in daily living. Reductions in dyskinesia and daily ‘off’ periods are also accounted for by the DBS. There are QOL-related improvements with DBS, including improved enjoyment of life, better fluidity of movement and improved walking.

The STN is the most common target for DBS in PD, but the posterior subthalamic area (PSA), including the caudal zona incerta (cZI), have also
been suggested as targets for DBS in PD. Similar improvements in motor symptoms have been seen in PSA DBS. Plaha et al. performed a non-randomized sequential study comparing cZI DBS to STN DBS (n=36) where cZI DBS had better limb outcomes compared to STN DBS.

**Deep Brain Stimulation and swallowing function**

Swallowing difficulties have been reported as an adverse effect in a small proportion of patients undergoing STN DBS. Liang et al. performed a prospective long-term study of 33 PD patients with STN DBS, where five out of these 33 patients (15%) developed chronic swallowing difficulties as an adverse effect following DBS surgery. Bejjani et al. reported that the swallowing parameter of the UPRS-III was unaffected by STN DBS. Most of these studies reported and examined a variety of different complications, and swallowing is not assessed optimally.

To date, there are three studies examining pharyngeal swallowing function with and without STN DBS. All three studies used video fluoroscopy to examine swallowing function. The Ciuccu et al. study included 14 patients examined postoperatively without medication with DBS stimulation turned on and off. Results showed that the pharyngeal transit time was shorter with STN DBS turned on, concluding that the pharyngeal phase was improved with stimulation on, while the oral phase was unaffected by DBS. Aspiration and penetration scores showed trends for decrease with the STN DBS turned on, but no significant difference were noted.

Lengerer et al. examined swallowing function in 18 patients. The assessments were done preoperatively and approximately 20 months postoperatively, with the STN DBS stimulation turned on as well as off (medication on). The results showed small improvement with stimulation on, but the changes were so small that the clinical relevance was considered very limited. The conclusion from the Lengerer et al. study was that STN DBS does not impair swallowing function.

Silbergleit et al. drew the same conclusion based on examinations from 14 patients. There was a small positive trend concerning motor control for solid consistencies and oral preparation of thin liquids due to stimulation without L-dopa medication. None of the other parameters were affected by STN DBS. Patients in the Silbergleit et al. study however reported their swallowing as improved after surgery measured by the Dysphagia Handicap Index.
Troche et al. critically reviewed all available studies including swallowing and DBS\textsuperscript{97}. Three additional studies are described in the review\textsuperscript{73,98,99}. The conclusion from the Troche et al. review was that due to methodological issues in the included studies, there are still gaps in our understanding of the effect of DBS on swallowing function, and more research needs to be conducted. Since STN is the predominant target for DBS, the studies mentioned above all focused on swallowing function after STN DBS.

The effect of cZI DBS on swallowing function has not previously been examined or reported in the literature. Reports of dysphagia as an adverse effect following cZI DBS are also limited\textsuperscript{84}. The cZI study included in this thesis is the only study to date focusing on swallowing function in cZI DBS.
Aim of the study

The aim of the studies in this thesis was to improve our understanding of the effect of cZI and STN DBS on pharyngeal swallowing function. Specific aims were to compare DBS effects over time postoperatively (6 & 12 months) for swallowing function, on and off stimulation, with a preoperative baseline assessment in order to identify possible negative swallowing effects of DBS.

Specific questions were the following:

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

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

3) Does cZI DBS have an effect on swallowing-related QOL?
Materials and methods

Participants

The two studies in this thesis included consecutive PD patients from the Northern region of Sweden selected for surgical treatment by the neurosurgical team at Umeå University Hospital according to internationally accepted inclusion and exclusion criteria for DBS (CAPSIT-PD)\textsuperscript{100}. The cZI patients are included in a larger research trial at Umeå University Hospital examining the outcomes of cZI DBS. Patients had been selected on clinical grounds for DBS surgery based on assessment of overall motor function, and swallowing status was not particularly assessed in the consideration for surgery. All patients were diagnosed with Idiopathic Parkinson’s disease according to the \textit{United Kingdom Parkinson’s Disease Society Brain Bank Criteria}\textsuperscript{101}. Patients with tremor dominant symptoms as well as non-tremor dominant symptoms were included. None of the patients had anticholinergic medication. Patients gave written informed consent, and the study was conducted in accordance with the Helsinki declaration. Ethical approval for the two studies was given by the regional Ethics board in Umeå (no. 08-093M).

Study I – Caudal zona incerta

Six males and two females were included in the cZI-study. The ages ranged between 49 and 71 years with a median age of 62 years. Median duration of disease was 6.5 years (range 2-12). Preoperatively, the median UPDRS III\textsuperscript{102} score was 35.5 (range 29-58) \textit{off} medication and 20.0 (range 10-42) \textit{on} medication. The surgical procedure and the cZI target have been described earlier\textsuperscript{82}. Indication for surgery and medication are seen in Table 1. All patients were bilaterally operated.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Indication for surgery</th>
<th>Stimulation</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>rigidity/bradykinesia</td>
<td>bilateral</td>
<td>L-Dopa, pramipexole</td>
</tr>
<tr>
<td>2</td>
<td>on-off fluctuations</td>
<td>bilateral</td>
<td>L-Dopa, pramipexole, entacapone, rasagiline</td>
</tr>
<tr>
<td>3</td>
<td>tremor</td>
<td>bilateral</td>
<td>L-Dopa</td>
</tr>
<tr>
<td>4</td>
<td>tremor</td>
<td>bilateral</td>
<td>L-Dopa, pramipexole</td>
</tr>
<tr>
<td>5</td>
<td>tremor</td>
<td>bilateral</td>
<td>L-Dopa, pramipexole, entacapone</td>
</tr>
<tr>
<td>6</td>
<td>on-off fluctuations</td>
<td>bilateral</td>
<td>L-Dopa, pramipexole</td>
</tr>
<tr>
<td>7</td>
<td>tremor</td>
<td>bilateral</td>
<td>L-Dopa, pramipexole, entacapone</td>
</tr>
<tr>
<td>8</td>
<td>tremor</td>
<td>bilateral</td>
<td>L-Dopa, pramipexole</td>
</tr>
</tbody>
</table>
Study II – Subthalamic nucleus Deep Brain Stimulation

The STN-study included eleven patients, eight males and three females. The ages ranged between 41 and 72 years with a median age of 61 years. Median duration of disease was 6.5 years (range 1-13). Preoperatively, the median UPDRS III score was 39.0 (range 19-57) off medication and 21.0 (range 4-57) on medication. None of the patients used anti-cholinergic medications. Video material from FEES was analyzed in 8 of 11 patients; three patients were included only in the analysis of patients’ self-assessments, due to incomplete or missing FEES video material. Implantations in the STN were uni- or bilateral. Indication for surgery and L-dopa equivalent dose are seen in Table 2.

Table 2 Main indication of surgery, stimulation and L-dopa equivalent dose

<table>
<thead>
<tr>
<th>Patient</th>
<th>Indication for surgery</th>
<th>Stimulation</th>
<th>L-dopa equivalent dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>tremor right hand</td>
<td>unilateral left</td>
<td>300 mg</td>
</tr>
<tr>
<td>2</td>
<td>tremor, on-off fluctuations, dyskinesia</td>
<td>bilateral</td>
<td>1428 mg</td>
</tr>
<tr>
<td>3</td>
<td>tremor right side</td>
<td>unilateral left</td>
<td>705 mg</td>
</tr>
<tr>
<td>4</td>
<td>wearing-off, dyskinesia</td>
<td>bilateral</td>
<td>654 mg</td>
</tr>
<tr>
<td>5</td>
<td>tremor bilateral</td>
<td>bilateral</td>
<td>1396 mg</td>
</tr>
<tr>
<td>6</td>
<td>tremor bilateral</td>
<td>unilateral right</td>
<td>744 mg</td>
</tr>
<tr>
<td>7</td>
<td>on-off fluctuations</td>
<td>bilateral</td>
<td>1064 mg</td>
</tr>
<tr>
<td>8</td>
<td>tremor right side, wearing-off</td>
<td>unilateral left</td>
<td>919 mg</td>
</tr>
<tr>
<td>9*</td>
<td>tremor right side</td>
<td>unilateral left</td>
<td>885 mg</td>
</tr>
<tr>
<td>10*</td>
<td>tremor bilateral</td>
<td>bilateral</td>
<td>2145 mg</td>
</tr>
<tr>
<td>11*</td>
<td>on-off fluctuations, dyskinesia</td>
<td>bilateral</td>
<td>1267 mg</td>
</tr>
</tbody>
</table>

*Only data from the self-estimations, no FEES parameters.

Procedure

The procedure and material was the same for Study I and Study II, except for the swallowing-related QOL questions included in Study I. Patients were evaluated in six different conditions. The preoperative conditions were medication off (medications withheld for 12 hours) and medication on (1.5 times the ordinary L-dopa dose). Postoperative conditions at six and 12 months were stimulator off and stimulator on, both with optimal ordinary L-dopa medication.

It would have been methodologically preferable to include medication off-stimulation on and medication off-stimulation off conditions. Such a design
was not considered ethically justifiable since the discomfort associated with *medication off* state is significant and the patients performed a range of different tests and evaluations during a couple of days. Other assessments were UPDRS, balance, neuropsychological tests and extensive evaluations of the individual electrode contacts etc. Due to the number of tests, and number of days required for these, it was considered necessary to limit the number of study days off medication after surgery.

**Evaluation of swallowing**

The FEES examinations were performed using an Olympus ENF P4 transnasal flexible endoscope and a Wolf endocam 5502. Test FEES test meal consisted of four liquid consistencies and one solid consistency, all coloured with green dye. The bolus size was one table spoon (10 ml) and the liquid consistencies were 50 ml water (C1), 50 ml water and 5 ml jellification powder (C2), 50 ml water and 10 ml jellification powder (C3), and 50 ml water and 15 ml jellification powder (C4). The solid consistency (C5) was a biscuit with a smear of C4 on top. Patients were given the food according to a standardized procedure.

Swallowing function was evaluated according to a predefined swallowing protocol. The swallowing protocol included parameters for aspiration (Rosenbek’s Penetration-aspiration scale), secretion (Secretion Severity Scale), pharyngeal residue, pharyngeal clearance, and preswallow spillage. Pharyngeal residue was operationalized as residue in the piriform sinuses or valleculae, and pharyngeal clearance as no residue after deglutition. Preswallow spillage was operationalized as green bolus seen before white-out. The video recordings were de-identified and randomized for order before the study assessment. Fifteen percent of the material was evaluated by a second author to ensure inter-rater reliability.

After the FEES test meal, the patients were asked to evaluate their swallowing function by putting a mark on a lineal visual analogue scale (Figure 2). One end of the scale represents 100 % functional swallowing and the other endpoint represented total loss of swallowing function. This measure was called percentage deterioration of the swallowing function (%DSF).

![Visual analogue scale used for self-assessments of swallowing function](image-url)
In Study 1, patients also answered swallowing-related QOL questions. They were asked if they had problems such as “affected swallowing function”, coughing when eating, consistency modification, weight loss, decreased mealtime pleasure, sticky saliva/hemming or drooling. Rating options were as follows: “Not at all”, “a little”, “often” or “a lot”. No Swedish version of SWAL-QOL was available at the time of the study\textsuperscript{105}.

Data and statistical analysis

A mean score from the five test meal consistencies was calculated for each and one of the different swallowing parameters. This score was used when examining the effect of cZI and STN DBS. The scores for penetration, preswallow spillage, pharyngeal residue and pharyngeal clearance were shifted by one so that the lowest score was always zero. The transformed Penetration/Aspiration scale then ranged from 0 to 7 points. Pharyngeal residue, preswallow spillage and clearance had a full range of 0-1 and Secretion Scale ranged between 0-3.

To find statistically significant differences between conditions, Friedman repeated measures test by ranks were used. Wilcoxon signed rank test was used for pair-wise post-hoc testing. P-values <.05 were considered statistically significant for identifying differences in comparisons. The statistical analyses were performed using the SPSS software package.
Results

Study I – Caudal zona incerta Deep Brain Stimulation

Descriptive data of individual Penetration/Aspiration scores are presented in Table 3. Aspiration was not observed in any of the eight patients.

Table 3 Individual presentation of penetration for different consistencies. Number of consistencies within two different categories of Penetration/Aspiration scale.

<table>
<thead>
<tr>
<th>Preoperative</th>
<th>Test dose L-dopa</th>
<th>6m Postoperative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penetration</td>
<td>Penetration</td>
<td>Penetration</td>
</tr>
<tr>
<td>Mild</td>
<td>Vocal folds</td>
<td>Mild</td>
</tr>
<tr>
<td>2-3p</td>
<td>4-5p</td>
<td>2-3p</td>
</tr>
<tr>
<td>Pat 1</td>
<td>-</td>
<td>C2, C3, C4</td>
</tr>
<tr>
<td>Pat 2</td>
<td>C4</td>
<td>-</td>
</tr>
<tr>
<td>Pat 3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pat 4</td>
<td>C2−C3</td>
<td>C3</td>
</tr>
<tr>
<td>Pat 5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pat 6</td>
<td>C4</td>
<td>-</td>
</tr>
<tr>
<td>Pat 7</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pat 8</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

12m Postoperative

| Penetration | Penetration | Penetration | Penetration |
| Mild        | Vocal folds | Mild        | Vocal folds |
| 2-3p        | 4-5p        | 2-3p        | 4-5p        |
| Pat 1        | C2          | -           | -           |
| Pat 2        | C4          | -           | C4          |
| Pat 3        | C4          | C2          | C3, C4      |
| Pat 4        | C3          | C2, C3      | -           |
| Pat 5        | -           | -           | -           |
| Pat 6        | C4          | -           | -           |
| Pat 7        | -           | C3          | -           |
| Pat 8        | -           | -           | -           |

Penetration Mild: bolus penetrates the laryngeal vestibule above vocal folds, scale score 2-3p. Penetration VOCAL folds: bolus contacts the vocal folds, scale score 4-5p. C1−C4: liquid consistencies; C5: solid consistency.

Preoperatively no changes were found between test dose of L-dopa and medication off for any of the swallowing parameters (p>0.05). Results from the statistical tests and medians for the specified test conditions are seen in Table 4. Brackets mark post-hoc differences.
Table 4  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.

<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></td>
<td>Med off</td>
<td>Test dose of L-dopa</td>
<td>Stim off</td>
<td>Stim on</td>
</tr>
<tr>
<td>P/A</td>
<td>0.2 (2.4)</td>
<td>0.4 (1.6)</td>
<td>0.2 (1.4)</td>
<td>0.3 (1.8)</td>
</tr>
<tr>
<td>Phr</td>
<td>0.6 (1.0)</td>
<td>0.5 (1.0)</td>
<td>0.6 (1.0)</td>
<td>0.3 (1.0)</td>
</tr>
<tr>
<td>PS</td>
<td>0.6 (1.0)</td>
<td>0.9 (0.4)</td>
<td>0.5 (1.0)</td>
<td>0.6 (0.8)</td>
</tr>
<tr>
<td>CC</td>
<td>0.5 (1.0)</td>
<td>0.5 (1.0)</td>
<td>0.7 (1.0)</td>
<td>0.3 (1.0)</td>
</tr>
<tr>
<td>SS</td>
<td>0.5 (2.0)</td>
<td>1.0 (2.0)</td>
<td>1.5 (3.0)</td>
<td>0.0 (2.0)</td>
</tr>
<tr>
<td>%DSF</td>
<td>22.5 (98.0)</td>
<td>23.0 (98.0)</td>
<td>23.5 (40.0)</td>
<td>18.0 (44.0)</td>
</tr>
</tbody>
</table>

P/A: Penetration and Aspiration scale, 0-7 p. Phr: pharyngeal residual, 0-1 p. PS: preswallow spillage, 0-1 p. CC: clearance, 0-1 p. SS: Secretions scale, 0-3 p. %DSF: Self-reported percentage deterioration of swallowing function, 0-100%. * \(p < .05\), post-hoc testing.

Comparisons between preoperative test dose of L-dopa and postoperative stimulation on and stimulation off revealed a postoperative reduction of preswallow spillage at six months in both on and off stimulation condition (\(z=-2.27\) and \(p=.02\), \(z=-2.047\) and \(p=.04\), respectively).

Postoperatively at six months, no differences for any of the swallowing parameters were seen between stimulation on and stimulation off, \(p>.05\) (medication on). At 12 months postoperatively, more preswallow was found in the stimulation on condition compared to the stimulation off (\(z=-2.070\), \(p=.04\) (medication on). There were no differences for the other swallowing parameters at 12 months postoperatively (\(p>.05\)).

Self-assessments

No differences in the %DSF were found between the testing conditions (Table 4). Similarly, there were no differences between testing conditions regarding the responses to the swallowing-related QOL questions (Table 5).
Table 5 Answers to the swallowing-related QOL questions. Scores 0-3p. The lower score the better the function

<table>
<thead>
<tr>
<th></th>
<th>Median (Range) Preoperative</th>
<th>6m Postoperative</th>
<th>12m Postoperative</th>
<th>Friedman’s test (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Affected swallowing</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. Consistency modification</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. Weight loss</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. Coughing when eating</td>
<td>0.0 (2.0)</td>
<td>0.0 (0.0)</td>
<td>0.0 (0.0)</td>
<td>4.00 p=.16</td>
</tr>
<tr>
<td>5. Decreased mealtime pleasure</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. Sticky saliva/Hemming</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. Drooling</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>

Study II – Subthalamic nucleus Deep Brain Stimulation

Descriptive data of %DSF, Penetration/Aspiration scores, and UPDRS III scores are seen in Table 6. Individual descriptive data from the Penetration/Aspiration scale are presented in Table 7. Statistical testing and group medians are seen in Table 8. Post-hoc statistical comparisons of %DSF are shown in Table 9.

Table 6 Individual data for %DSF, Penetration/Aspiration and UPDRS-III scores

<table>
<thead>
<tr>
<th>%DSF</th>
<th>Preoperative</th>
<th>6m Postoperative</th>
<th>12m Postoperative</th>
<th>Penetration and aspiration scores</th>
<th>Preoperative</th>
<th>6m Postoperative</th>
<th>12m Postoperative</th>
<th>UPDRS-III</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Med off</td>
<td>Test dose</td>
<td>Stim off</td>
<td>Stim on</td>
<td>Med off</td>
<td>Test dose</td>
<td>Stim off</td>
<td>Stim on</td>
</tr>
<tr>
<td>1</td>
<td>25</td>
<td>20</td>
<td>5</td>
<td>16</td>
<td>30</td>
<td>15</td>
<td>2.8</td>
<td>0.0</td>
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<tr>
<td>2</td>
<td>53</td>
<td>27</td>
<td>46</td>
<td>35</td>
<td>76</td>
<td>65</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>28</td>
<td>25</td>
<td>3</td>
<td>8</td>
<td>19</td>
<td>0.0</td>
<td>0.6</td>
</tr>
<tr>
<td>4</td>
<td>32</td>
<td>11</td>
<td>39</td>
<td>23</td>
<td>14</td>
<td>8</td>
<td>0.0</td>
<td>0.4</td>
</tr>
<tr>
<td>5</td>
<td>34</td>
<td>10</td>
<td>3</td>
<td>1</td>
<td>15</td>
<td>11</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>2</td>
<td>49</td>
<td>7</td>
<td>6</td>
<td>3</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>7</td>
<td>26</td>
<td>14</td>
<td>24</td>
<td>10</td>
<td>25</td>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>8</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>25</td>
<td>8</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>9</td>
<td>0</td>
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<td>11</td>
<td>6</td>
<td>52</td>
<td>31</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>48</td>
<td>38</td>
<td>40</td>
<td>35</td>
<td>44</td>
<td>27</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>71</td>
<td>53</td>
<td>34</td>
<td>5</td>
<td>19</td>
<td>6</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mean</td>
<td>25.4</td>
<td>18.9</td>
<td>25.4</td>
<td>13.1</td>
<td>28.5</td>
<td>17.4</td>
<td>0.5</td>
<td>0.2</td>
</tr>
</tbody>
</table>

%DSF= self-reported percentage deterioration of swallowing function
**Table 7** Individual presentation of penetration for different consistencies. Number of consistencies within three different categories of Penetration/Aspiration scale

<table>
<thead>
<tr>
<th>Consistency</th>
<th>Penetration Mild</th>
<th>Penetration Vocal folds</th>
<th>Aspiration 6-8p</th>
</tr>
</thead>
<tbody>
<tr>
<td>c1-c4</td>
<td>M</td>
<td>M</td>
<td>4</td>
</tr>
<tr>
<td>c5</td>
<td>S</td>
<td>S</td>
<td>5</td>
</tr>
</tbody>
</table>

**Table 8** 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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Median (Range)</th>
<th>Friedman test (n=8-11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P/A</td>
<td>Preoperative</td>
<td>6m Postoperative</td>
</tr>
<tr>
<td>Penetration and Aspiration scale</td>
<td>0.1 (0.8)</td>
<td>0.0 (0.8)</td>
</tr>
<tr>
<td>Phr</td>
<td>0.2 (0.6)</td>
<td>0.0 (0.2)</td>
</tr>
<tr>
<td>Phr</td>
<td>0.0 (1.0)</td>
<td>0.0 (0.8)</td>
</tr>
<tr>
<td>CC</td>
<td>0.0 (1.0)</td>
<td>0.0 (0.8)</td>
</tr>
<tr>
<td>SS</td>
<td>0.5 (2.0)</td>
<td>0.0 (2.0)</td>
</tr>
<tr>
<td>%DSF</td>
<td>26.0 (71.0)</td>
<td>14.0 (55.0)</td>
</tr>
</tbody>
</table>

P/A: Penetration and Aspiration scale, 0-7p. Phr: Pharyngeal residual, 0-1p. PS: Preswallow spillage, 0-1p. CC: clearance, 0-1p. SS: Secretions Severity Scale, 0-3p. %DSF: Self-reported percentage deterioration of swallowing function, 0-100%.

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Penetration Mild: bolus penetrates the laryngeal vestibule above vocal folds, scale score 2-3p. Penetration Vocal folds: bolus contacts the vocal folds, scale score 4-5p. Aspiration: bolus passes below vocal folds, scale score 6-8p. c1-c4: liquid consistencies, c5: solid consistency.
Table 9: Pairwise comparison of %DSF. Median and range. Preoperatively, 6 months and 12 months after surgery. The lower scores the better the function. N=11

<table>
<thead>
<tr>
<th></th>
<th>Preoperative</th>
<th>6m Postoperative</th>
<th>12m Postoperative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Med off</td>
<td>Test dose of L-dopa</td>
<td>Stim off</td>
</tr>
<tr>
<td>Median (Range)</td>
<td>26.0 (71.0)</td>
<td>14.0 (55.0)</td>
<td>25.0 (46.0)</td>
</tr>
<tr>
<td>Preop</td>
<td>Med off</td>
<td>-</td>
<td>p=.01</td>
</tr>
<tr>
<td></td>
<td>Test dose</td>
<td>14.0 (55.0)</td>
<td>n.s</td>
</tr>
<tr>
<td>6m</td>
<td>Stim off</td>
<td>25.0 (46.0)</td>
<td>n.s</td>
</tr>
<tr>
<td></td>
<td>Stim on</td>
<td>7.0 (34.0)</td>
<td>p=.01</td>
</tr>
<tr>
<td>Postop</td>
<td>Stim off</td>
<td>25.0 (70.0)</td>
<td>n.s</td>
</tr>
<tr>
<td></td>
<td>Stim on</td>
<td>11.0 (65.0)</td>
<td>n.s</td>
</tr>
</tbody>
</table>

Value is significant at \( p<.05 \) (two-tailed). Wilcoxon signed rank test. \( n.s \): Non significant.

Preoperatively, the subjective measure of %DSF was improved with test dose of L-dopa compared to medication off (\( z=-2.50, p=.01 \)). Swallowing parameters Penetration/Aspiration, Secretions, pharyngeal residual, preswallow spillage, and clearance showed no changes between test dose of L-dopa and medication off (\( p>.05 \)).

Comparison between preoperative medication off and six months postoperative stimulation on revealed improvement in the subjective evaluation of the swallowing function (\( z=-2.49, p=.01 \)). There were no differences between test dose of L-dopa and stimulation on at six and 12 months, \( p>.05 \). No differences between pre- and postoperative condition were observed regarding the swallowing parameters from the FEES.

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

**Intra- and inter-rater reliability**

In Study 1, intra-rater reliability was 95%, and Kappa scores for intra-rater reliability and inter-rater reliability were .88 and .72. In Study 2, both inter- and intra-rater reliability was 95%, and all parameters had similar levels of agreement.
Analysis

The aim of this thesis was to provide a better understanding of the effect of cZI and STN DBS on pharyngeal swallowing function. The first specific research question asked was whether cZI and STN DBS had an effect on pharyngeal swallowing parameters. The results from the two studies included were consistent. Neither cZI DBS nor STN DBS had a significant effect on overall swallowing function in the patients included in the two studies. The occurrence of aspiration, secretion, pharyngeal residue and clearance was not affected by the DBS. There was only one observed negative effect of cZI stimulation (Study I) in the postoperative conditions. More preswallow spillage was observed with the stimulation turned on compared to off at 12 months postoperatively. However, the amount of preswallow spillage with stimulation on at 12 months was not worse than before the operation.

The second specific research question was how self-estimated swallowing function was affected by cZI and STN DBS. The self-estimations measured by %DSF did not show any differences between conditions in the cZI group (Study I). Thus the cZI patients did not experience any effect of operation itself or the stimulation on their swallowing function. In the STN sample (Study II), the patients’ self-estimation measured by %DSF revealed that they experienced improved swallowing due to STN DBS when comparing stimulation on and stimulation off.

The third specific research question was whether or not swallowing-related QOL is affected by cZI DBS. The results show that the QOL was neither affected by the operation itself nor by the stimulation in the postoperative conditions.
Discussion

The two studies showed that STN and cZI DBS did not have a negative effect on the swallowing function in the two groups studied. The conclusions from these two studies are similar to the conclusions from Ciucci et al., Lengerer et al., and Silbergleit et al., where no negative effects of DBS were found. This is a positive result in light of the findings from Liang et al., which reported that 15% (5/33 patients) of the STN DBS-operated PD patients in their cohort reported chronic swallowing difficulties as an adverse effect following DBS operation.

The results available in the studies of Ciucci et al., Lengerer et al. and Silbergleit et al. show small improvements or trends of positive swallowing outcomes. These improvements were not replicated in our STN DBS study. A difference between our STN DBS study and the studies of Ciucci et al. and Silbergleit et al. is that their postoperative examinations were done with medication off while ours were done with medication on. This methodological aspect makes it difficult to compare data between these studies since the medication might mask possible positive effects. In the Silbergleit et al. study, the improvement with stimulation on compared to stimulation off disappeared when medication was on. However, one could argue that improvements which are manifested only in medication off state are of limited clinical value.

Another difference between the discussed studies that might affect the outcomes is that the previous DBS swallowing studies used video fluoroscopy to examine swallowing function while our study used FEES.

The FEES data from both the STN and the cZI sample showed that the swallowing problems were mild. In the cZI sample (Study I), none of patients showed signs of aspiration. In the STN sample (Study II), aspiration was evident in 3 out of 240 instances. Lengerer et al. and Ciucci et al. found similar scenarios with only mild swallowing changes in the PD patients selected to DBS. When interpreting the results from this thesis, it is important to remember that the swallowing problems in these two samples were mild and cannot be generalized to patients with severe dysphagia.

There have been suggestions that swallowing function might be well preserved in the early stages of PD, and the estimated onset of dysphagia has been proposed to be up to 130 months (10.8 years). In this sense, the two samples (STN and cZI) included in this thesis had short disease durations (median 6.5 years). In the Liang et al. study, with 15% of patients...
having dysphagia after DBS, the mean disease duration was 11.9 years\textsuperscript{92}. Ciucci et al. and Silbergleit et al. did not report disease duration, while Lengerer et al. reported the disease duration to be 135 months (11.3 years). As swallowing function might be related to overall disease duration, it is important to investigate the effect of DBS on patients with long disease durations. The forthcoming studies in the research area have to follow the DBS-operated patients’ swallowing function over time. It is also important to discuss disease durations when comparing studies.

The patients in the STN sample (Study II) reported that their swallowing function had improved with DBS, although FEES examinations did not confirm positive changes. Consequently, there was a discrepancy between the self-estimated swallowing function and the ratings from the FEES. Discrepancies between subjective and objective measures are common and have been observed in dysphagic patients\textsuperscript{38–42,107}. The discrepancy in this study is different, though, since the subjective measure indicates an effect of a specific treatment, while the objective measure does not. Silbergleit et al. observed a similar discrepancy as the patients estimated their swallowing as better over time, even though the video fluoroscopy did not reveal any clear improvements\textsuperscript{96}. Silbergleit et al. presented several possible explanations for the disparity, and some of them might be relevant in our study as well. One possible explanation for the discrepancy in our study could be that the improvements experienced by the patients were not manifested in the examined pharyngeal phase, but rather in the oral or esophageal stages of the deglutition. Thus, they could not have been observed using our FEES protocol.

A second explanation might be that improvements experienced by the patients are inconsistent or evident only across time. Such subtle changes are not likely to be recognized in a 30 minutes FEES examination including only a few consistencies and a limited number of swallows. Baijens et al. described a similar discrepancy between subjective perception of swallowing function and measures from video fluoroscopy\textsuperscript{48}. They were unable to present differences regarding swallowing function between early stage PD patients complaining about dysphagia, and healthy elderly controls without dysphagic complaints\textsuperscript{48}.

Finally, a third explanation could be that improvements in overall motor function due to DBS may have an effect on patient perception of their swallowing function. In that way, overall improvements could have led to a more positive estimation of the swallowing function, even if the swallowing function itself was unaffected by the DBS stimulation. This possibility is also discussed in Silbergleit et al.\textsuperscript{96}. 

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The results from the swallowing-related QOL questions are in agreement with the other measures from the cZI sample; no differences were seen among conditions.

**Strengths and limitations of the study**

The prospective study design, with examinations pre- and postoperatively, was a strength in the two studies in this thesis. The same examination protocol was employed for all examinations, and this enabled an analysis of possible differences between pre- and postoperative stages. Ciucci et al. only examined swallowing postoperatively, while Lengerer et al. based their conclusions on retrospective data with variable time spans after DBS operation and swallowing examinations\(^{94,95}\). The study conducted by Silbergleit et al. included both pre- and postoperative examinations\(^{96}\).

The study design with self-estimations, FEES measures, as well as swallowing-related QOL questions (Study I) is more robust than objective measures alone. Another advantage is that the swallowing protocols employed were well validated, and that intra- and inter-rater reliability was controlled\(^{108}\).

The number of patients is a limitation in the two studies. If additional patients could have been included, the studies would have had more power to detect differences. The sex distribution (5 females and 14 males) in the two samples also has to be taken into consideration in the interpretation of the results. A greater proportion of males undergo DBS surgery, and the reasons for this is not known and needs further investigation\(^{109}\).

A limitation in the study design was that all postoperative examinations were performed with medication on. As a result, the effect of DBS cannot be completely separated from the impact of the medication. The decision to maintain medication on during examinations was based on ethical considerations.

**Future research and clinical implications**

To explore the effect of DBS on swallowing function in PD patients with moderate to severe dysphagic problems, further research needs to be conducted. A cohort-matched control study design has the methodological strength that there is some control for disease progression. It is important to include objective as well as subjective measures in future studies, since one of my studies found a discrepancy between the measures. Future research including video fluoroscopy or manometry would give complementary
information about the effect of DBS on the oral and esophageal phases of deglutition. This thesis focused on measures from the pharyngeal phase.

Study I is so far the only study that has examined the swallowing function after cZI DBS, and this makes the results very important. The sample is relatively small and the swallowing difficulties minor, so it is important to be cautious when interpreting the results.

The clinical implications from this thesis are that PD patients with mild swallowing problems seem to be able to undergo STN or cZI DBS without increasing the risk of pharyngeal swallowing difficulties.

**Conclusion**

DBS in STN and cZI did not have a substantial negative effect on swallowing function. Patients with STN DBS appear to experience self-perceived improvement in swallowing function with DBS. There was no increased risk for aspiration or penetration due to surgery or stimulation regardless of stimulation site. As the samples in these studies are small, these findings need to be confirmed by further investigation.
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