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Balance performance in people with Parkinson’s disease

Effects of subthalamic Deep Brain Stimulation

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List of publications

I. Nilsson MH, Törnqvist A.L, Rehncrona S.
Deep-brain stimulation in the subthalamic nuclei improves balance performance in patients with Parkinson’s disease, when tested without anti-parkinsonian medication.

II. Nilsson MH, Jarnlo G-B, Rehncrona S.
Functional balance performance in patients with Parkinson’s disease after long-term treatment with subthalamic nucleus high-frequency stimulation.

III. Nilsson MH, Fransson PA, Jarnlo G-B, Magnusson M, Rehncrona S.
Balance performance and fear of falling in patients with Parkinson’s disease treated with high frequency subthalamic stimulation.

IV. Nilsson MH, Rehncrona S, Jarnlo G-B.
Fear of falling and falls in people with Parkinson’s disease treated with Deep Brain Stimulation in the subthalamic nuclei.
Manuscript.
Abstract

Balance impairment is one of the most distressing symptoms in Parkinson’s disease (PD). Compared with age-matched controls, people with PD have an increased risk of falling and a fear of falling is usually common. The balance impairment remains a limitation despite the use of anti-PD medication. Anti-PD medication (levodopa) is initially very effective, but complications can occur after 5-8 years. The effect then seems less effective and can fluctuate, and side effects (e.g. hyperkinesia) can develop.

Deep Brain Stimulation (DBS) is a neurosurgical and complementary treatment option. Electrodes are inserted into the brain, most commonly in the subthalamic nuclei (STN). The electrical stimulation is computer programmed and can be regulated for optimal effect or turned off. In daily life, the stimulation is ongoing.

DBS in STN both reduces PD-symptoms and the need for anti-PD medication. However, the effect on balance remains unclear. The studies presented in this thesis are the first to prospectively and systematically evaluate the effects of DBS in STN on functional balance performance, fear of falling and falls in people with PD.

This thesis comprises four original Papers. In three of these the participants were evaluated both before and after surgery (Papers I, II and IV). Paper I included 31 participants who were followed up at 6 & 12 months, Paper II included 28 participants with a 1 & 3-year follow-up, and Paper IV included 20 participants with a 1-year follow-up. In Paper III the ten participants were evaluated on an average of 37 months after surgery.

The effect of STN stimulation alone was investigated in Papers I, II and III. The participants were evaluated after an overnight withdrawal of anti-PD medication. Evaluations were conducted both with the stimulation turned off and on, respectively. Functional balance performance was evaluated with the Berg balance scale (BBS): 0-56 points, higher scores: “better” balance. With the STN stimulation turned on, the BBS-scores were significantly improved both at 6 and 12 months after surgery.

When evaluated without any treatment (no anti-PD medication and the stimulation turned off), the scores of the BBS had deteriorated at the three-year follow-up (Paper II). This indicates that the treatment did not prevent
functional balance performance from decreasing over time. Despite this, STN stimulation alone had a remaining positive effect three years after surgery. The effect of STN stimulation alone was also investigated in a study with ten participants (Paper III). The scores of the BBS significantly increased. A majority of the timed tests (e.g. increased gait speed) also showed improvements. Furthermore, the participants rated their fear of falling as decreased. Force-plate measurements (posturography) were also conducted. These results showed no statistical significant differences, which may be a consequence of the limited sample size.

All in all, the results of Papers I, II and III showed that STN stimulation alone had a positive effect on functional balance performance both at the short and long-term follow-ups.

A combined treatment is used in daily life, i.e. reduced anti-PD medication and STN stimulation. The dosage of anti-PD medication was reduced by 53% three years after surgery (Paper II). Anti-PD medication further improved the BBS-scores as compared with the effect of STN stimulation alone. The evolution of the combined treatment effect was investigated in Paper II. When comparing the results (before surgery, 1 year, 3 years), the scores of the BBS were lower (“worse”) at three years. The difference was close to statistical significance.

In Paper IV the participants registered falls (fall-diary) both before and after surgery. The rate of falls was not significantly different after surgery. Further and larger studies are warranted to support or refute this finding. One year after surgery, the participants rated themselves as having a decreased fear of falling during more complex activities. The ratings furthermore indicated decreased activity avoidance due to the risk of falling. This indicates a positive effect on activities and participation.
Svensk sammanfattning
(SUMMARY IN SWEDISH)

Vid Parkinsons sjukdom (PS) är balanspåverkan ett av de mest begränsande symtomen. Personer med PS har en ökad fallrisk jämfört med andra i samma ålder och även en mer uttalad rädsla för att falla. Balanspåverkan kvarstår även vid behandling med läkemedel.

Initialt har behandling med läkemedel (levodopa) god effekt, men efter 5-8 år inträder ofta den så kallade komplikationsfasen. Medicinen upplevs då inte verka fullt ut, dess effekt skifter och personerna kan få biverkningar såsom överrörlighet.


Studierna i denna avhandling är de första som systematiskt undersökt STN-stimuleringens effekt avseende funktionell balansförmåga, rädsla för att falla och fallfrekvens.

Avhandlingen innefattar fyra delarbeten. I tre av dessa utvärderades deltagarna före och efter operation (delarbeten I, II och IV). Delarbete I omfattade 31 deltagare med 6 och 12 månaders uppföljning, delarbete II omfattade 28 deltagare med 1 och 3 års uppföljning och delarbete IV omfattade 20 deltagare med 12 månaders uppföljning. I delarbete III utvärderades 10 deltagare i genomsnitt 37 månader efter operation.


När individerna utvärderades utan någon behandling (ingen medicin och stimuleringen av) så var resultaten på BBS försämrade vid långtidsuppföljningen (delarbete II). Detta indikerar att behandlingen inte


I delarbete IV registrerade individerna förekomsten av fall med hjälp av en falldagbok. Detta utfördes både före och efter operation. Fallfrekvensen visade inga statistiska skillnader efter operationen vilket borde utredas vidare i större studier. Ett år efter operation ansåg individerna sig ha en lägre rädsla för att falla i mer komplexa aktiviteter. Skattningarna indikerade även att deltagarna i minskad utsträckning undvek aktiviteter på grund av en risk för att falla. Detta tyder på en positiv effekt både vad gäller aktiviteter och delaktighet.
Thesis at a glance

<table>
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<tr>
<th>Study I</th>
<th>31 participants</th>
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<tbody>
<tr>
<td>Aim</td>
<td>To investigate how balance performance responded to STN stimulation when tested without anti-PD medication.</td>
</tr>
<tr>
<td>Methods</td>
<td>Tests were conducted without anti-PD medication (i.e., overnight withdrawal) at 6 and 12 months after surgery. The Berg balance scale &amp; &quot;the postural stability test&quot; (Item 30, UPDRS III) were assessed both with the STN stimulation turned off and on.</td>
</tr>
<tr>
<td>Results</td>
<td>Both at 6 and 12 months, the results of the Berg balance scale &amp; Item 30 were statistically improved when the STN stimulation was turned on.</td>
</tr>
<tr>
<td>Conclusions</td>
<td>When tested without anti-PD medication, STN stimulation improves functional balance performance and &quot;postural stability&quot;.</td>
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<th>Study II</th>
<th>20 participants</th>
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<tr>
<td>Aim</td>
<td>To investigate if balance performance was affected by long-term treatment of STN stimulation.</td>
</tr>
<tr>
<td>Methods</td>
<td>The Berg balance scale was assessed before as well as 1 and 3 years after surgery: with and without anti-PD medication and STN stimulation turned off and on.</td>
</tr>
<tr>
<td>Results</td>
<td>Without any treatment (no medication &amp; stimulation turned off), the scores of the Berg balance scale aggravated over time. Three years after surgery, the scores still improved when turning the stimulation on. Anti-PD medication added to this effect.</td>
</tr>
<tr>
<td>Conclusions</td>
<td>Although balance performance decreased over time, functional balance performance was positively affected by STN stimulation. Anti-PD medication added to this effect.</td>
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<tr>
<th>Study III</th>
<th>10 participants</th>
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<tr>
<td>Aim</td>
<td>To explore the effect of STN stimulation on balance performance as assessed with clinical performance tests, posturography and subjective ratings of fear of falling.</td>
</tr>
<tr>
<td>Methods</td>
<td>Testing was conducted without anti-PD medication, and with the STN stimulation turned off and on (start randomized).</td>
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<tr>
<td>Results</td>
<td>STN stimulation improved (statistically) the results of all clinical tests, except sharpened Romberg. The subjective ratings showed an increased fall-related self-efficacy. Three participants did not manage posturography when the STN stimulation was turned off, but all did so when it was turned on. The posturography results of the seven participants with complete data showed no significant differences, but it may be caused by the small sample size.</td>
</tr>
<tr>
<td>Conclusions</td>
<td>In this sample, STN stimulation alone significantly improved the results of the clinical performance tests that mimic activities in daily living. This improvement was further supported by the patients' ratings of fear of falling, which was less severe with the STN stimulation turned ON. The posturography results of the seven participants with complete data showed no significant differences due to STN stimulation.</td>
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<thead>
<tr>
<th>Study IV</th>
<th>20 participants</th>
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<tbody>
<tr>
<td>Aim</td>
<td>To explore how fear of falling and falls were affected one year after surgery.</td>
</tr>
<tr>
<td>Methods</td>
<td>Fear of falling was evaluated with questionnaires- before and one year after surgery. Falls were prospectively recorded (fall diary) both before and after surgery.</td>
</tr>
<tr>
<td>Results</td>
<td>One year after surgery, the participants rated themselves as having a lower activity avoidance and having an increased fall-related self-efficacy in more complex activities. The fall rate showed no significant difference.</td>
</tr>
<tr>
<td>Conclusions</td>
<td>After surgery, the scores that related to fear of falling showed improvements which indicate positive effects on activities and participation. This study can not support any change in fall rate after surgery, which could be caused by the small sample size. Further studies are warranted.</td>
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<tr>
<td>Abbreviations</td>
<td>Description</td>
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<td>---------------</td>
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<tr>
<td>BBS</td>
<td>Berg balance scale</td>
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<tr>
<td>CNS</td>
<td>Central Nervous System</td>
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<tr>
<td>COG</td>
<td>Centre of Gravity</td>
</tr>
<tr>
<td>COM</td>
<td>Centre of Mass</td>
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<tr>
<td>DBS</td>
<td>Deep Brain Stimulation, DBS OFF/ON: DBS is turned off/on.</td>
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<tr>
<td>FES(S)</td>
<td>Falls-Efficacy scale, Swedish version</td>
</tr>
<tr>
<td>FOF</td>
<td>Fear of falling</td>
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<td>IADL</td>
<td>Instrumental Activities of Daily Living</td>
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<td>ICC</td>
<td>Intraclass Correlation Coefficient</td>
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<tr>
<td>ICF</td>
<td>International Classification of Functioning, Disability and Health</td>
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<td>IPG</td>
<td>implanted pulse generator</td>
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<tr>
<td>FOG</td>
<td>freezing of gait</td>
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<td>GPI</td>
<td>globus pallidus internus</td>
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<tr>
<td>L-dopa</td>
<td>levodopa. LED: L-dopa Equivalent Doses</td>
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<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<tr>
<td>Nm</td>
<td>Newton-meter</td>
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<tr>
<td>PADL</td>
<td>Personal Activities of Daily Living</td>
</tr>
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<td>PD</td>
<td>Parkinson’s disease</td>
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<td>PPN</td>
<td>pedunculopontine nucleus</td>
</tr>
<tr>
<td>q1-q3</td>
<td>first and third quartiles</td>
</tr>
<tr>
<td>r_s</td>
<td>Spearman rank order correlation coefficient</td>
</tr>
<tr>
<td>SAFFE</td>
<td>modified Survey of Activities and Fear of Falling in the Elderly</td>
</tr>
<tr>
<td>SD</td>
<td>standard deviation</td>
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<tr>
<td>SDD</td>
<td>Smallest Detectable Difference</td>
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<tr>
<td>SR</td>
<td>sharpened Romberg</td>
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<tr>
<td>STN</td>
<td>nucleus subthalamicus</td>
</tr>
<tr>
<td>TUG</td>
<td>Timed Up &amp; Go test</td>
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<tr>
<td>VIM</td>
<td>ventrointermediol nucleus of thalamus</td>
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<tr>
<td>UPDRS</td>
<td>Unified Parkinson’s disease Rating Scale (part III: motor examination)</td>
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### Definitions

<table>
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<th>Term</th>
<th>Description</th>
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<tr>
<td><strong>Balance</strong></td>
<td>Balance is “a generic term describing the dynamics of body posture to prevent falling”, Winter (1995). Balance is interpreted as a broad term (an umbrella term), Ragnarsdóttir (1996).</td>
</tr>
<tr>
<td><strong>Combined treatment</strong></td>
<td>relates to the treatment after DBS in STN. It consists of a reduced dosage of anti-PD medication and a continuous STN stimulation.</td>
</tr>
<tr>
<td><strong>Defined on</strong></td>
<td>Participants are evaluated after administering an individually standardized dose of levodopa, which is delivered after an overnight withdrawal of anti-PD medication, Defer et al. (1999).</td>
</tr>
<tr>
<td><strong>Fall</strong></td>
<td>“an unexpected event in which the participants come to rest on the ground, floor or other lower level”, Lamb et al. (2005).</td>
</tr>
<tr>
<td><strong>Fear of falling</strong></td>
<td>The construct of fear of falling (FOF) can be described as an ongoing concern about falling, a loss of balance confidence, low fall-related self-efficacy or as activity avoidance. FOF could either be related to balance in general or more specifically to the risk of falling. It can be assessed by using patient-reported outcomes which provide the individuals’ perceptions of their functions and/or how activities and participation are affected. Fall-related self-efficacy and activity avoidance are evaluated within this thesis.</td>
</tr>
<tr>
<td><strong>Functional balance performance</strong></td>
<td>Functional balance comprises postural control and equilibrium control, Huxham et al. (2001). Functional balance performance is thus interpreted as a broader term. The term is used when describing the Berg balance scale, Berg et al. (1989).</td>
</tr>
<tr>
<td><strong>Near fall</strong></td>
<td>“a fall initiated but arrested by support from a wall, railing, other person etc”, Gray and Hildebrandt (2000).</td>
</tr>
</tbody>
</table>
**Off condition/state**  
In general, this could relate to when the effect of anti-PD medication is lacking. Within research, this relates to when the participants are evaluated after an overnight (10-12 hours) withdrawal of anti-PD medication, i.e. “practically defined off”, Defer et al. (1999).

**On condition/state**  
when anti-PD medication is effective and symptoms are well controlled.

**Postural instability**  
The term is used when describing one of the four cardinal symptoms in PD. It is also used when describing the results of item 30 (Postural stability) of the UPDRS.

**“STN stimulation alone”**  
the effect of STN stimulation when the participants are evaluated without anti-PD medication. Within this thesis comparisons are done after surgery: STN stimulation turned off versus on.
Introduction

I. Balance

The success of maintaining balance emerges from the interaction of the individual, the task and the environment. Several individual factors influence this, such as physical functioning, cognitive resources (including attention) and balance confidence. Balance control depends on the ability to adapt as the requirements change and on the strategies used to accomplish stability. It is essential when performing activities in our daily life.

For a human (on earth), the maintenance of posture in standing is challenged by several factors. We have to counteract gravitational forces, about 2/3 of our body mass is located above the waist, and the feet constitute a relative small contact area with the ground. Posture could be described as the biomechanical alignment of the body or as “the orientation of any body segment relative to the gravitational vector”. Postural muscle tone is the prime contributor in maintaining vertical stance.

There is not a universal definition of balance, and nor a consensus of when to use the term “postural control” or “balance control”. Several do use the terms (postural control, balance control, equilibrium, postural stability) synonymously, e.g. postural stability is according to Shumway-Cook and Woollacott also referred to as balance.

Massion and Wollacott described postural control to mainly involve two tasks: the maintenance of upright stance and the maintenance of equilibrium. Berg described that balance control constitutes three dimensions: the maintenance of a specified posture, adjustments to voluntary movements and reactions to external disturbances.

Several definitions relate to maintaining the Centre of Gravity (COG) within the limits of stability as determined by the base of support. The base of support includes the person’s points of contacts with the supporting area and the area between these points. COG is “the vertical projection onto the ground of the body’s Centre of Mass (COM)” defined as a point that is at the centre of the total body mass, and it is “the weighed average of the COM of each body segment”. The COG moves outside the base of support during walking.
Balance has been considered “a generic term describing the dynamics of body posture to prevent falling” \(^9\), and as an umbrella term which incorporates postural control \(^11\). Others described determinants of functional balance to comprise postural control and equilibrium control \(^6\). In accordance, functional balance performance is interpreted as a broader term.

Some divide the definition of balance to comprise static and dynamic balance. Static balance has been defined as “the ability to maintain the COG within a base of support in a quiet upright position during standing or sitting” \(^15\). That is, “sitting and/or standing quietly” \(^1\). The term static is however somewhat misleading since we have postural sway also in quiet stance. Dynamic balance has been defined as “maintaining balance while moving” \(^16\), and it thus includes walking \(^17\).

Balance disturbances or perturbations can either be external (caused by the environment, e.g. a push) or internal, i.e. elicited by self-generated movements \(^6, 9\). Unpredicted external perturbations lead to reactive responses whereas internal perturbations require an anticipatory (predictive) control \(^9\). In daily life, perturbations are usually caused by self-generated movements and balance is generally challenged because of turning, bending or reaching \(^9\).

**Resources**

There is not a single system that controls balance, but several systems that interact \(^1, 5\). Since balance is not controlled by a single system, the maintenance requires a complex interaction between the musculoskeletal and nervous system \(^16\). Some musculoskeletal components of importance are range of motion and flexibility. In order to be able to maintain balance we need adequate somatosensory, vestibular and visual information. The Central Nervous System (CNS) rapidly integrates and processes the data from the different receptor systems. CNS employs both feedforward (predictive or anticipative) and feedback (reactive) control to compensate for balance perturbations during movements.

Horak highlighted six important resources required for postural stability and orientation \(^5\):
- Biomechanical resources. If having for example limited strength, range of motion or sensory information, this could serve as biomechanical constraints and affect the ability to detect the limits of stability.
- Movement strategies, which can be reactive, anticipatory and/or voluntary. Reactive strategies include “fixed-support” strategies and/or “change-in-support” strategies. Prior experiences and expectations influence the response.
- Sensory strategies, which involve integrating sensory information (somatosensory, visual, vestibular) and re-weighting this information if required by the environment.
- Orientation in space of the body with respect to gravity, support surface, and internal references.
- “Control of dynamics”, which involves maintaining balance during gait and transfers.
- Cognitive processing, which includes attention, motivation and emotional aspects. More cognitive resources are required as the difficulty of the task increases.

**Assessments of balance**

The International Classification of Functioning, Disability and Health (ICF) (developed by the World Health Organization) can serve as a framework and it will be described later on.

Aspects related to balance can be evaluated by using clinical tests, laboratory assessments (e.g. posturography), and by using patient reported outcomes. In comparison with laboratory assessments, clinical tests are easy to administer, less expensive, need no sophisticated equipment, can reflect daily activities and may be performed in the participants’ own home.

The advantages of posturography tests are that they allow a standardized and reproducible procedure of using external balance perturbations as well as offering a quantification of the postural responses. Perturbations can then be evoked in various ways including tilting the support surface or by using vibratory stimulation. Vibration applied to a muscle increases the afferent signals from the muscle spindles and creates a proprioceptive illusion that the vibrated muscle is being stretched.

Patient-reported outcomes provide the individuals’ perceptions of their functions and/or how activities and participation are affected.
The utmost sign of disturbed balance is falls and subsequent injuries and fractures, which may cause high costs for the individuals as well as for the society.

**Falls**

Normal aging is characterized by a decline in the systems involved in maintaining balance. Approximately 30% of community-dwelling people aged 65 and older fall at least once a year, and most falls occur during walking.

In 2005 the Prevention of Falls Network in Europe published a consensus statement of outcomes when investigating falls. A clear definition of a fall was recommended: “an unexpected event in which the participants come to rest on the ground, floor or other lower level”. This definition is used within this thesis.

Falls were advocated to be registered prospectively by using daily recording. Telephone interviews or face-face interviews were recommended to rectify missing data and for clarifying the circumstances of the falls. Studies relying on retrospective recall of falls are less reliable.

Single falls are more likely to be caused by temporary circumstances and are less likely than recurrent falls (at least two falls) to reflect underlying neurological or balance problems.

Risk factors for falls can be broadly classified into two categories: intrinsic factors (relate to the individual) and extrinsic factors, which relate to the environment. Falls have a multi-factorial aetiology with numerous risk factors including having gait and balance impairments, and/or having a neurological disorder such as Parkinson’s disease.
II. Parkinson’s disease

Parkinson’s disease (PD) is a progressive neurodegenerative disorder. It is characterized by the degeneration of dopaminergic neurons in the substantia nigra, which results in the loss of dopamine. Several areas within the brain and brain stem are however affected 29, 30.

The mean age of onset is usually in the mid or late 60s 31-33. About 5% develop clinical signs before an age of 50 years 31, 33. Approximately 1-2 % of the population over 65 years suffers from PD. Most prevalence studies in Europe found crude prevalence rates of PD between 100 and 200 per 100 000 inhabitants 33, 34. The age-adjusted prevalence was 76 per 100 000 in a Swedish study conducted in 1989 35. A systematic review reported age-standardized incidence rates ranging from 8.4 to 19 per 100 000 inhabitants 32. Studies generally report a higher prevalence and greater incidence of PD in men than in women 31-34. Taylor et al. stated that men are about 1.5 times more likely to develop PD than women 36.

Standardized clinical criteria are used when diagnosing PD 37, 38 since autopsy is needed to confirm a definite one. The aetiology still remains unclear. Several mechanisms have been considered as contributing factors including genetic and environmental factors such as pesticides 39.

Influences on functioning, activities and participation

PD is characterized by four cardinal signs: tremor at rest, rigidity, akinesia (or bradykinesia) and postural instability 40.

Tremor at rest (4-6 Hz) is reduced or ceased during the execution of movements, and it is more prominent in the distal part of an extremity. Rigidity is characterized by an increased resistance in muscle tone while passively moving a joint (both while bending and extending) 40, 41. Akinesia is an absence of movements and incorporates the inability to initiate movements. Bradykinesia means slowness of movements while hypokinesia signifies decreased amplitude and a scarcity of movements 40, 42. An asymmetrical onset of motor symptoms is classical for PD 42. Postural instability will be described in more detail further on. Prominent postural instability and falls within the
first three years after symptom onset speak in favour of an alternative diagnosis \(^{37,39}\).

Several other motor features can be present including having difficulties getting up from a chair, rolling over in bed and turning around \(^{43-46}\). About 50\%-60\% of people with PD have difficulties turning around while walking \(^{43,45,46}\).

An impaired gait is common, and it was reported by 75\% of those with a PD-duration of at least five years \(^{44}\). The shuffling gait with reduced ground clearance is associated with a decreased arm-swing \(^{40}\). In comparison with age-matched controls, people with PD have for example a decreased gait speed and a reduced step length \(^{47-51}\). About one third or more of people with PD experience sudden and transient motor blocks (freezing) while initiating or performing activities \(^{52}\). Freezing of gait (FOG) is often described as if the feet were glued to the floor. It appears when initiating the first step (start hesitation), when turning or when approaching a target (destination hesitation or “target freezing”) \(^{52,53}\). FOG is usually evoked in crowded and confined spaces as well as when having limited time, e.g. when crossing a street. It typically occurs as sudden and short lasting (<10s) episodes at home, which makes it difficult to observe and assess during clinical testing and in laboratory settings \(^{43,54}\). Severe FOG in the early stage of PD is atypical \(^{55}\).

People with PD may also have difficulties in performing sequential and repetitive tasks as well as performing simultaneous tasks \(^{45,49,56-59}\).

A stooped posture (trunk and knees are flexed) generally occurs later in the disease \(^{40,60}\). The trunk can also be laterally flexed (“postural lean”) \(^{60}\).

Non-motor symptoms are also featured such as neuropsychiatric symptoms (e.g. dementia, depression, apathy, anxiety, cognitive dysfunction), sleep dysfunction (e.g. insomnia), autonomic symptoms (e.g. bladder disturbances, postural hypotension), gastrointestinal symptoms (e.g. constipation), sensory symptoms (e.g. pain) and fatigue \(^{61}\).

The main focus of this thesis is on balance.
III. Balance, falls and fear of falling in people with PD

Postural instability is one of the most distressing symptoms in PD. It marks the transition between mild to moderate PD as defined by the Hoehn & Yahr staging. The Hoehn and Yahr stages range from I–V (a higher stage is more severe), and stage III incorporates mild to moderate disability.

Stage III: “The first sign of impaired righting reflexes. This is evident by unsteadiness as the patient turns or is demonstrated when he is pushed from standing equilibrium with the feet together and eyes closed”.

People with PD are particularly unstable when perturbed backwards. Almost two thirds of those with a PD-duration of at least five years experienced postural instability with falls.

Turning during an everyday task evokes instability in two thirds of those with severe PD (Hoehn & Yahr stage IV). The true figure might be even higher due to the study’s dropout. Already those with mild PD have an impaired turning. That is, they start rotating their head later than controls and the trunk is almost simultaneously turned. In other words, people with PD orientate their gaze towards the new direction later than controls.

In comparison with age-matched controls, the onset of rotation is delayed. While turning, people with PD take more and slower steps with a narrower step width. Those having severe PD require even more steps. The turning angle is smaller and about 75% of the angle used by healthy elderly. Even those with mild or with no rigidity have an impaired turning.

Postural instability has been reported to be the major cause for falling in PD. Postural instability and falls negatively influence health related quality of life. It may result in hospital and nursing home admissions and cause an increased burden on caregivers.

Falls
After diagnosis, the time to the first fall has been reported to be about nine to twelve years.
At present, only four studies (full length articles) prospectively and systematically registered falls in people with PD without evaluating an ongoing intervention \cite{45,71,74,84}. In these studies, 51%-68% of the participants reported falls, whereas 25%-51% fell at least twice (recurrent fallers). The two studies with the longest follow-up period (12 months) reported the highest number of fallers (63%-68%) as well as recurrent fallers \cite{74,84}. A meta-analysis showed that the best predictor of falling was two or more falls in the previous year (sensitivity 68%; specificity 81%) \cite{85}.

**Circumstances of falls**

People with PD mostly fall while ambulant and most frequently during walking \cite{71,86}. Walking has been reported in connection with 54% of all falls \cite{71}. Falls have also been related to turning, reaching tasks and while bending forward \cite{45,46,71,86,87}. Falling during transfers has most commonly been connected with standing up or sitting down \cite{45,71,86}. People with PD have difficulties in performing simultaneous tasks \cite{45,49,57-59}, and carrying something while ambulating is connected with falls \cite{86,87}.

Bloem et al. reported that 70% of the falls were due to intrinsic factors, and less than 15% of the falls were due to slipping or tripping \cite{45}. Most of the falls happen indoors at home \cite{45,74,86,87}, which approximately accounts for 80% of all falls \cite{45,86}. Falling forward was mentioned twice as often as falling either backwards or sideways \cite{87}. The direction of falls in everyday life has otherwise rarely been systematically reported. Being in a confined space was reported in connection with 36% of all falls \cite{71}. The peak time for falls was about two hours after medications \cite{71}. Most of the falls (about 60-67%) occur in the “on state”, i.e. when medication is effective and symptoms well controlled \cite{45,71}.

**Near falls**

It is also common for people with PD to experience near falls. A near fall has been defined as “an occasion on which an individual felt that they were going to fall but did not actually fall” \cite{87}. Gray and Hildebrand defined it instead as “a fall initiated but arrested by support from a wall, railing, other person etc” \cite{71}. The latter definition is used within this thesis. Approximately 60-75% of people with PD experience near falls, and it is common also among those who do not fall (60-62%) \cite{87,88}. 


**Injuries and fractures in relation to falls**

Studies have reported an increased risk for fractures in PD \(^{89-91}\) and hip fractures are most frequently reported \(^{82, 90-92}\). Prospective follow-up studies of falls have yielded somewhat diverging results. Although 32%-62% of all falls resulted in injuries, most of them were connected with soft tissue injuries, i.e. scrapes, bruises and bumps \(^{45, 71, 74}\). Bloem et al., reported no fractures during a six-month follow-up \(^{35}\). Another study reported that 1.2 % out of 736 falls (during one year) resulted in fractures \(^{74}\).

**Fear of falling**

Conceptually, the construct of fear of falling (FOF) has been described as an ongoing concern about falling, a loss of balance confidence, low fall-related self-efficacy or as activity avoidance \(^{93-97}\). FOF and decreased balance confidence is more frequent in people with PD, and it is more pronounced than in healthy controls \(^{4, 45, 98}\). It can be experienced also among those with PD who do not fall. FOF is however more common and pronounced in fallers and even more so in recurrent fallers \(^{99-103}\). Approximately 60% of the 119 included participants expressed a FOF, but it increased to 76 % among those who reported previous falls \(^{99}\).

FOF can result in restrictions in daily activities and cause social isolation \(^{45, 104}\).

It is recommended to include an assessment of FOF when investigating falls and balance impairment, which also has been specifically recommended for people with PD \(^{4, 25, 105}\). Falls-Efficacy scale (FES) was originally developed by Tinetti et al. and it was designed to assess “the degree of perceived efficacy at avoiding a fall during each of 10 relatively nonhazardous activities of daily living” \(^{94, 95}\). The definition is based on Banduras work, who states that “perceived self-efficacy is a judgment of one’s capability to accomplish a certain level of performance” \(^{106}\).

The Survey of Activities and Fear of Falling in the Elderly was developed by Lachman et al. \(^{96}\). It was later on modified by Yardley et al., and this version is referred to as SAFFE \(^{97}\). SAFFE measures activity avoidance due to the risk of falling.

In people with PD, postural instability and falls are at least partly due to non-dopaminergic lesions and are considered to be less responsive to anti-PD medication \(^{107-109}\). This warrants for additional treatment options.
IV. Treatments for Parkinson’s disease

Levodopa (L-dopa) is still the most effective symptomatic anti-PD drug, although after a few years of treatment it is associated with motor complications, i.e. fluctuations and dyskinesia \(^{110}\). Several other oral drugs are used such as: dopamine agonists, Cathecol-O-methyltransferase (COMT) inhibitors, monoamine oxidase isoenzyme type B (MAO-B) inhibitors, amantadine and to some extent anticholinergics drugs \(^{111,112}\). There exist other options to oral delivery such as continuous enteral infusion, which requires a portable pump \(^{113}\).

In addition to pharmacological treatment, rehabilitation is important and may include occupational therapy, physical therapy and speech therapy. A theoretical framework supporting physical therapy in PD was first described by Meg Morris \(^{41}\). In 2007 an evidenced based review identified six specific core areas for physical therapy in PD: transfers, posture, reaching and grasping, balance and falls, cueing strategies to improve gait, physical capacity and activity \(^{114}\). This review has currently been updated \(^{115}\) to also include recommendations about high force eccentric muscle training \(^{116}\).

Meg Morris underlines that physical therapists have an important role in evaluating the effects of different interventions including both pharmacological treatment and brain surgery \(^{117}\).

Symptomatic neurosurgical treatment options exist, which include lesions and Deep Brain Stimulation (DBS). The latter is the predominating option at present.

**Deep Brain Stimulation**

The DBS system consists of three parts: the insulated lead (electrode), an insulated extension wire and the implanted pulse generator (IPG). The lead is inserted through a small opening in the skull and the tip of the electrode is positioned within the targeted brain area. The extension wire is then connected and passed under the skin to the battery-operated IPG. The IPG is placed under the skin below the clavicle, and it can be externally programmed. The electrical stimulation can thus be turned on or off as well as adjusted: polarity, amplitude (V), pulswidth (µs) and frequency (Hz).

The surgical procedure can slightly vary, and the procedure used in Lund will be described in more detail further on.

For people with PD several optional targets for DBS are used e.g. the ventrointermedial nucleus of thalamus (VIM), the globus pallidus internus
(GPI), the subthalamic nucleus (STN) and more lately also the pedunculopontine nucleus (PPN). STN is currently the most commonly used target for bilateral DBS in PD. This thesis investigates those treated with bilateral STN stimulation.

**STN stimulation**

A stable condition of DBS-parameter settings is usually reached within three to six months after surgery. In daily life, the vast majority is treated with a combined treatment, i.e. reduced dosage of anti-PD medication and a continuous STN stimulation. After surgery and when tested with the combined treatment, the results of motor symptoms are generally comparable to the “on state” prior to surgery. The need for pharmacological treatment is significantly reduced after surgery. At long-term follow-ups (3-5 years), the dosage of anti-PD medication was reduced by 29%-35% or close to or above 50% or close to or above 50% or close to or above 50%. Dyskinesia, motor fluctuations and the time spent in off periods are reduced after surgery.

A meta-analysis showed that STN stimulation alone (without anti-PD medication) reduced motor symptoms by 52% as compared with before surgery. The mean follow-up time of the 34 included studies was 15 months (ranging from six months to five years). STN stimulation effectively controls motor symptoms even three to five years after surgery.

The advantages of STN stimulation over oral treatment with L-dopa is that it allows a continuous treatment without fluctuating effects due to changing plasma L-dopa levels. The mechanism of action of STN stimulation is not fully understood. Several mechanisms are probably involved in creating a functional inhibition of the overactive target.

**Predictive factors of motor outcome, adverse events & side effects**

Studies have shown that L-dopa responsiveness on motor symptoms prior to surgery is a predictive factor for motor outcome after surgery. A meta-analysis showed that the largest motor changes after surgery was seen in patients that before surgery, they had more severe motor symptoms, were L-Dopa responsive in motor symptoms and had longer disease duration. Some studies suggested that a younger age at surgery predicted a better
motor outcome 118, 132, 133, 135, whereas other studies did not support this 130, 134, 136.

The risk of surgery itself is generally considered to be small. The risk of a haemorrhage or an infection is below 4% 130. Device related complications have been reported to be below 5% 130.

Many of the reported side effects or adverse events after surgery coincide with advanced PD and could be elicited by the reduction of dopaminergic drugs 122-124, 127. Among the most frequently reported side effects after surgery is speech disturbance 118, 119, 123, 125, 127, 129, 130, 137. Weight gain has frequently been reported 118, 119, 122, 124, 125, 127, 129, 130. In a four-year follow-up, cognition/memory decline and psychiatric disturbances were the most common reported adverse event after surgery 137. This finding is also reported by others 123, 129.

Gait and balance disturbances have also been reported. In the multicenter study by Hariz et al., two out of the four most commonly reported adverse events included gait and balance disturbances 137. Others have also reported gait and/or balance impairment to be among the four most common side effects 119, 123. Welter et al. suggested that those with gait and balance disorders should be weighted carefully before selected for surgery 133.

The above studies mainly base their concerns about gait and balance on single items within the Unified Parkinson’s Disease Rating Scale (UPDRS) 138. The majority of clinical long-term studies have mainly investigated the effect on balance by using a single item of UPDRS part III, i.e. item 30 (postural stability) 119, 122, 123, 127, 129. A single item will most likely not capture the complexity of balance. It is furthermore of importance to also include assessments incorporating activities as well as participation. No previous study did prospectively evaluate the effect of STN stimulation on functional balance performance, fear of falling and falls.
Aims of the Thesis

- To investigate how balance performance in patients with PD responded to DBS in the STN if tested without anti-parkinsonian medication. The secondary aim was to compare the results of balance performance to the test of postural stability (UPDRS, item 30).
  **Paper I**

- To prospectively investigate if functional balance performance of patients with Parkinson’s disease (PD) was affected by long-term (three years) treatment with bilateral STN stimulation, either alone or in combination with anti-PD medication. The evolution of functional balance performance over time was also explored.
  **Paper II**

- To explore the effects of STN stimulation alone on balance performance as assessed with clinical performance tests, subjective ratings of fear of falling and posturography.
  **Paper III**

- The primary aim was to prospectively explore how fear of falling and fall rate in people with PD were affected after treatment with STN stimulation. Secondarily, we wished to investigate if fall rate after surgery had any relationship to the participant’s characteristics before surgery. In addition, we wished to descriptively explore the circumstances of the falls in more detail.
  **Paper IV**
Participants

All participants were recruited from the Department of Neurosurgery, Lund University Hospital. During the time period of recruiting (Table 1), all those with PD who were selected for bilateral STN stimulation were consecutively included into study I, II and IV.

Indications for surgery were unchanged throughout the course of the studies and they were: idiopathic PD, responsiveness to L-dopa but an insufficient clinical effect of the medication, and normal magnetic resonance imaging (MRI) of the brain. Exclusion criteria for surgery were cognitive decline and dementia. Screening for cognitive decline and dementia was thus performed prior to the selection of surgery by a neurologist and by at least one occupational therapist, and in some instances by a neuro-psychiatrist.

Study III had specific inclusion and exclusion criteria, which are presented below.

In Paper I, 35 participants were selected for surgery. Four of them were excluded from the present study: one had an incorrect or uncertain PD diagnose, two were unable to cooperate during testing (e.g. postural hypotension), and one had deceased (unrelated to surgery). Thirty-one participants were included.

In Paper II, 35 participants were selected for surgery. Seven of them were excluded from the study: one refused attending the follow-up, one had changed the DBS target during the follow-up, two had severe back-pain and awaited surgery, two participants were missed for follow-up, and one had deceased (unrelated to surgery). The excluded participants did not differ significantly (p>0.1, the Mann-Whitney U test) from the included ones with respect to age, duration of PD, motor symptoms or functional balance performance. Twenty-eight participants were included. Twelve of them had also participated in study I.

In Paper III, 25 patients (22 men, three women) with PD fulfilled the specific inclusion criteria of having been treated with bilateral STN stimulation for at least one year and being between 59-69 years old. Fourteen of them were excluded due to the following exclusion criteria: concomitant diseases or symptoms interfering with balance testing such as...
sensibility deficits in the lower extremities or severe pain (n=8), an inability to cooperate (n=2) or an inability to stand for two minutes without support (n=4). One patient declined participation. Ten participants were included. All of them had also participated in study I or study II or in both (n=1).

In Paper IV, 24 participants were selected for surgery. Three of them were excluded due to severe comorbidity that interfered with testing (two waited for surgery due to osteoarthritis in the lower extremities, and one had severe respiratory problems). Another participant was excluded due to an exchange of the DBS target. Twenty participants were included.

Sixty-seven different participants were included in Papers I-IV. Basic characteristics of the included participants (Papers I-IV) are presented in Table 1. For further details see the corresponding Papers. Information about the parameter settings (STN stimulation) and the active electrode localizations is to be found within the papers.

Ethical approval
The Research Ethics Committee at Lund University approved the studies. Written informed consent was given by the participants in Papers II, III and IV. Informed oral consent was given for participation in Paper I.
Table 1. Characteristics of the participants in Papers I-IV

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>23 men</td>
<td>25 men</td>
<td>9 men</td>
<td>13 men</td>
</tr>
<tr>
<td>Age, years</td>
<td>Median (min-max)</td>
<td>65 (50-77)</td>
<td>63 (49-75)</td>
<td>66 (59-69)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>65 (7.2)</td>
<td>62 (6.5)</td>
<td>65 (3.7)</td>
<td>65 (6.4)</td>
</tr>
<tr>
<td>PD duration, years</td>
<td>Median (min-max)</td>
<td>14 (7-30)</td>
<td>14 (7-30)</td>
<td>18 (10-22)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>15 (6.2)</td>
<td>15 (5.5)</td>
<td>17 (3.8)</td>
<td>13 (4.6)</td>
</tr>
<tr>
<td>L-dopa equivalents (mg/day) Mean (SD)</td>
<td>1100 (860)</td>
<td>1240 (663)</td>
<td>479 (228)</td>
<td>1057 (406)</td>
</tr>
</tbody>
</table>

Clinical assessments before surgery

<table>
<thead>
<tr>
<th>UPDRS part III</th>
<th>Median (q1-q3)</th>
<th>Min-max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without anti-PD medication</td>
<td>41 (30-49)</td>
<td>10-74, n=30</td>
</tr>
<tr>
<td>10-74, n=30</td>
<td>40 (31-50)</td>
<td>19-66</td>
</tr>
<tr>
<td>With anti-PD medication</td>
<td>Not applicable</td>
<td>18 (14-29)</td>
</tr>
<tr>
<td>The Berg balance scale</td>
<td>Not applicable</td>
<td>45 (43-50)</td>
</tr>
<tr>
<td>Without anti-PD medication</td>
<td>45 (35-49)</td>
<td>0-54, n=30</td>
</tr>
<tr>
<td>0-54, n=30</td>
<td>49 (44-50)</td>
<td>22-53, n=26</td>
</tr>
<tr>
<td>With anti-PD medication</td>
<td>Not applicable</td>
<td>51 (48-53)</td>
</tr>
<tr>
<td>33-55, n=28</td>
<td>51 (48-53)</td>
<td>26-53, n=19</td>
</tr>
</tbody>
</table>

UPDRS part III: motor examination of Unified Parkinson’s Disease Rating Scale. The maximum total score is 108 points, and higher scores denote more severe motor symptoms. The maximum total score of the Berg balance scale (BBS) is 56 points, and higher scores denote “better” balance.

1 One participant was missed for the UPDRS assessment. Another one was missed for the BBS-assessment. 
2 Two out of 30 participants scored 0 on the BBS. 
3 Two participants were unable to perform the BBS when tested without anti-PD medication. 
4 Before surgery and with anti-PD medication, one participant was unable to perform the BBS due to a short lasting effect of medication.

Anti-PD medication was given as levodopa (L-Dopa) equivalents and was calculated according to Østergaard et al. and Calne.
Methods

Design
The participants were tested both before and after surgery (pre and post test design) in Papers I, II and IV. Paper I included a six-month follow-up and a one-year follow-up. In Paper II, evaluations were done both one and three years after surgery. Paper IV included a one-year follow-up. Paper III had a post-test design and the participants were evaluated at a mean follow-up of 37 months (min-max, 15-70) after surgery.

Settings
The participants were assessed as in-patients in all of the studies (Papers I-IV). All assessments in Papers I, II and IV were conducted at the same premises at the Department of Neurosurgery. The assessments in Paper III were done in a laboratory setting. Paper III was conducted in close collaboration with the Department of Otorhinolaryngology Head and Neck surgery, Lund University Hospital.

Test conditions
The participants were evaluated both when they had an effect of their anti-PD medication (“on condition”), and when they were without anti-PD medication (“off condition”).

Tests without anti-PD medication were always done in the morning after an overnight (10-12 hours) withdrawal of anti-PD medication (Papers I-IV).

Evaluations with anti-PD medication differed depending on what kinds of evaluations were done and by whom. Motor symptoms (UPDRS part III) were tested after administering an individually standardized dose of L-dopa (from 75 to 200 mg) (Papers II and IV). This was delivered on the same day and after the assessments had been completed in the “off condition”. The approximate same dosage of L-dopa was used both before and after surgery (Paper II). The participants were assessed when the medication was effective (approximately one hour after intake). The evaluation of motor symptoms (UPDRS, part III) was done by a neurologist or a specialized nurse (Papers I-IV). The two assessors were well experienced with the testing and scoring procedure, and they had previously performed assessments together. The physical therapist evaluated the participants when they subjectively felt at their
best with their ordinary anti-PD medication. This was never conducted on the same day as when the participants had been evaluated without anti-PD medication.

The effect of STN stimulation alone was assessed after surgery when the participants were without anti-PD medication (Papers I, II and III). Comparisons were done between the results with the STN stimulation turned off and on, respectively. This was conducted on two consecutive days (starting with STN stimulation turned off) in Papers I and II. In Paper III, the two test conditions were evaluated on the same day.

The evolution of functional balance performance over time was investigated in Paper II. The participants were then assessed without anti-PD medication. This was done both before and after surgery, and with the STN stimulation turned off after surgery.

When tested with the STN stimulation turned off, the stimulation was consequently turned off for 30 minutes before the testing was initiated (Papers I, II and III).

With the STN stimulation turned on, the stimulation had been turned on for at least 20 hours before the testing was initiated in Papers I and II. In Paper III, the stimulation had either been on for at least 20 hours or for 30 minutes depending on how the participants were randomized.

After surgery and in real life, a combined treatment is used, i.e. reduced anti-PD medication and an ongoing STN stimulation. The combined treatment effect was evaluated in Papers II and IV.

**Neurosurgical procedure**

In all patients surgery was performed at the Department of Neurosurgery, Lund University Hospital, Sweden, by one neurosurgeon. The Activa® DBS system (Medtronic inc, Minneapolis, Mn, USA) with quadripolar electrodes was used and the electrodes were implanted with the Leksell G-frame (Elekta AB, Stockholm, Sweden). Targeting was guided by intraoperative MRI. The images were exported to the Elekta Surgiplan stereotactic planning system for calculating the stereotactic target coordinates. Clinical effects on PD-symptoms as well as side-effects were tested intraoperatorively with the patients fully awake. MRI scanning was performed during sedation (Propofol). Implantations of pulse-generators and extensions cables were done under
general anaesthesia. Final plain stereotactic X ray verified the locations of the DBS electrode contacts.

The DBS systems were programmed within two days after surgery and optimized between the follow-up evaluations.

The participants were evaluated both before and after surgery by the Team for Functional Movement Disorders. The team includes neurosurgeons, neurologists, nurses, occupational therapist, physical therapist and assistant nurses.

After surgery and at discharge, the majority of the participants (Papers I-IV) received a referral for physical therapy.

**Outcome measures, equipments and related procedures**

The outcome measures (Papers I-IV) are presented based on different perspectives. Table 2 describes which measures are included within the respective Papers (I-IV). Table 3 briefly summarizes the measures with respect to what they measure, how it is measured and the scoring procedure. A schematic categorization of the included measures (Papers I-IV) using the ICF is presented in Figure 1.**
Table 2. Design of studies and outcome measures (Papers I-IV)

<table>
<thead>
<tr>
<th>Study design</th>
<th>Paper I</th>
<th>Paper II</th>
<th>Paper III</th>
<th>Paper IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up time after surgery</td>
<td>6 &amp; 12 months</td>
<td>1 &amp; 3 years</td>
<td>At least 1 year</td>
<td>1 year</td>
</tr>
<tr>
<td>Outcome measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berg balance scale</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Ten meter walk test</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Timed Up &amp; Go</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chair-stand test</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>One leg stance</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sharpened Romberg</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FES(S)</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>SAFFE</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Falls</td>
<td></td>
<td></td>
<td>Descriptive purpose, retrospective recall</td>
<td>X Prospective fall diary</td>
</tr>
<tr>
<td>Near falls</td>
<td></td>
<td></td>
<td>Descriptive purpose, retrospective recall</td>
<td>X Prospective fall diary</td>
</tr>
<tr>
<td>Posturography</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UPDRS part III (motor part)</td>
<td>X</td>
<td></td>
<td>Descriptive purpose</td>
<td>Descriptive purpose</td>
</tr>
<tr>
<td>Item 30, UPDRS part III (postural stability)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FES(S): Falls-Efficacy scale, Swedish version.
SAFFE: modified Survey of Activities and Fear of Falling in the Elderly.

1 Assessed or administered by the physical therapist. The same physical therapist (MHN) assessed all participants in Papers I-IV.
<table>
<thead>
<tr>
<th>Measure (Clinical, Patient reported, Laboratory)</th>
<th>What does it measure &amp;/ or how is it measured?</th>
<th>Scoring / registered result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berg balance scale</td>
<td>“Functional performance” with a focus on the</td>
<td>14 items graded from 0-4.</td>
</tr>
<tr>
<td></td>
<td>subject’s ability “to maintain balance when</td>
<td>Total score: 0-56 points.</td>
</tr>
<tr>
<td></td>
<td>asked to perform a series of movements” (Berg</td>
<td>Higher scores: “better”</td>
</tr>
<tr>
<td>Ten meter walk test</td>
<td>Gait speed</td>
<td>meter/seconds (m/s)</td>
</tr>
<tr>
<td></td>
<td>Walking distance (10m) divided by the total</td>
<td></td>
</tr>
<tr>
<td></td>
<td>time taken to complete the task.</td>
<td></td>
</tr>
<tr>
<td>Timed Up &amp; Go</td>
<td>Time to complete the following tasks: to rise</td>
<td>seconds (s)</td>
</tr>
<tr>
<td></td>
<td>from a chair, walk 3 m, turn around and walk</td>
<td></td>
</tr>
<tr>
<td></td>
<td>back to sit down again. Tests “basic mobility</td>
<td></td>
</tr>
<tr>
<td></td>
<td>skills” (Podsiadlo, 1991).</td>
<td></td>
</tr>
<tr>
<td>Chair-stand test</td>
<td>The time to rise from sitting to standing, 5</td>
<td>seconds (s)</td>
</tr>
<tr>
<td></td>
<td>times.</td>
<td></td>
</tr>
<tr>
<td>One leg stance</td>
<td>The time one is able to stand on one leg.</td>
<td>seconds (s)</td>
</tr>
<tr>
<td>Sharpened Romberg</td>
<td>The time one is able to stand with one foot</td>
<td>seconds (s)</td>
</tr>
<tr>
<td></td>
<td>just in front of the other (“tandem stance”).</td>
<td></td>
</tr>
<tr>
<td>UPDRS part III</td>
<td>“Motor examination” (Fahn, 1987). The severity</td>
<td>14 items: graded from 0-4.</td>
</tr>
<tr>
<td>Item 30, UPDRS part III</td>
<td>Postural stability - “the righting reflex”</td>
<td>Higher scores: more severe</td>
</tr>
<tr>
<td></td>
<td>(Fahn, 1987). Conducted in standing- a pull</td>
<td>motor symptoms.</td>
</tr>
<tr>
<td></td>
<td>on shoulders while prepared.</td>
<td></td>
</tr>
<tr>
<td>FES(S)</td>
<td>Fall-related self-efficacy. FES was originally</td>
<td>13 items (activities): graded</td>
</tr>
<tr>
<td></td>
<td>“designed to assess the degree of perceived</td>
<td>from 0-10</td>
</tr>
<tr>
<td></td>
<td>efficacy (i.e., self-confidence) at avoiding a fall” (Timetti, 1990).</td>
<td>PADL subscale (6 items):</td>
</tr>
<tr>
<td></td>
<td>The Swedish version is referred to as FES(S).</td>
<td>0-60 points.</td>
</tr>
<tr>
<td>SAFFE</td>
<td>The conceptual approach to fear of falling was</td>
<td>17 items (activities): Graded</td>
</tr>
<tr>
<td></td>
<td>“to focus on undesirable consequences of this</td>
<td>from 1-3.</td>
</tr>
<tr>
<td></td>
<td>fear (i.e. activity restriction])” (Lachman, 1998)</td>
<td>Total score: 17-51 points.</td>
</tr>
<tr>
<td></td>
<td>That is, activity avoidance due to a risk of</td>
<td>Higher scores: more avoidance</td>
</tr>
<tr>
<td></td>
<td>falling (Yardley 2002).</td>
<td></td>
</tr>
<tr>
<td>Falls</td>
<td>A fall is defined as an “unexpected event in</td>
<td>Number of fallers and</td>
</tr>
<tr>
<td></td>
<td>which the participant came to rest on the</td>
<td>recurrent fallers. Fall rate</td>
</tr>
<tr>
<td></td>
<td>ground, floor or other lower level” (Lamb,</td>
<td>Consequences and</td>
</tr>
<tr>
<td>Neear falls</td>
<td>A near fall is defined as a “fall initiated</td>
<td>Number who experience near</td>
</tr>
<tr>
<td></td>
<td>but arrested by support from a wall, railing,</td>
<td>falls. The rate of near falls.</td>
</tr>
<tr>
<td></td>
<td>other person, etc” (Gray and Hildebrand, 2000).</td>
<td></td>
</tr>
<tr>
<td>Posturography</td>
<td>Standing on a force platform, which detects</td>
<td>[Nm/(kg*m)^2] The values are corrected for differences in body</td>
</tr>
<tr>
<td></td>
<td>force variations. Torque variance corresponds to the amount of energy used to maintain standing.</td>
<td>constitutions.</td>
</tr>
</tbody>
</table>

Fig 1. A schematic overview of used outcome measures in relation to the International Classification of Functioning, Disability and Health (ICF) 20. Only outcome measures related to balance control are included in Figure 1, and no descriptive measures are included. The schematic categorization (overlapping of constructs exist) is inspired by the work by Lee Dibble et al. 141. The use and adaptation of the Figure is done with permission from the first author.

ICF contains two parts 20. Part I concerns “Functioning and Disability”. This part includes two components: 1) Body Functions and Structures (i.e. physiological functions of body systems and anatomical parts of the body), and 2) Activities and Participation.

“Activity is the execution of a task or action by an individual”, whereas “participation is involvement in a life situation”. Capacity describes an individual’s ability to execute a task or an action, whereas performance describes what an individual does in his/her own environment.

Part II conceptualizes contextual factors, which include environmental and personal factors.
The Berg balance scale

The Berg balance scale (BBS) 12, 142-144 was used as an outcome in all of the Papers. BBS assesses functional balance performance 12 of importance in daily life 142, 143. It is an ordinal scale including 14 items (Table 4), which are graded from 0 to 4. The score per item is reduced if the time and distance requirements are not met, and/or if supervision or assistance is required. Higher scores denote “better” balance performance. Performing the test takes about 15-20 minutes and requires a stopwatch, a ruler, a step stool, and two chairs. The assessment incorporates both balance performance in sitting and standing as well as dynamic balance performance, e.g. rising, reaching forward, turning around, and picking up an object from the floor. Balance is mainly challenged by self-generated perturbations or by a decreased base of support 6.

Berg and co-workers developed the content of the scale during three phases where 28% of the included participants had Parkinson’s disease 12. The BBS has been translated into Swedish by Lundin-Olsson et al. 144.

Table 4. Items of the Berg balance scale

<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sitting to standing</td>
</tr>
<tr>
<td>2</td>
<td>Standing unsupported for 2 minutes</td>
</tr>
<tr>
<td>3</td>
<td>Sitting unsupported for 2 minutes</td>
</tr>
<tr>
<td>4</td>
<td>Standing to sitting</td>
</tr>
<tr>
<td>5</td>
<td>Transfer from chair to chair</td>
</tr>
<tr>
<td>6</td>
<td>Standing unsupported with eyes closed for 10 seconds</td>
</tr>
<tr>
<td>7</td>
<td>Standing unsupported with feet together for 1 minute</td>
</tr>
<tr>
<td>8</td>
<td>Reaching forward with outstretched arm</td>
</tr>
<tr>
<td>9</td>
<td>Retrieving an object from the floor</td>
</tr>
<tr>
<td>10</td>
<td>Turning to look over shoulder, tested bilaterally</td>
</tr>
<tr>
<td>11</td>
<td>Turning 360 degrees in 4 seconds, tested in both directions</td>
</tr>
<tr>
<td>12</td>
<td>Placing alternative foot on a stool, 8 steps in 20 seconds</td>
</tr>
<tr>
<td>13</td>
<td>Standing with one foot in front of the other for 30 seconds</td>
</tr>
<tr>
<td>14</td>
<td>Standing on one leg for 10 seconds</td>
</tr>
</tbody>
</table>

Each item is graded from 0-4, maximum score is 56 points.

The BBS has proved to be both a valid, reliable and a responsive assessment of functional balance performance in people with PD. Intrarater reliability (Intraclass Correlation coefficient, ICC) has been reported to range between 0.87 (home environment) to 0.94 145, 146. Interrater reliability
was 0.74 (ICC) in the home environment. Cronbach’s alpha has ranged from 0.86 to 0.95 when tested with anti-PD medication. The item to total correlation values ranged from 0.62 (Item 10: turning to look over one’s shoulder) to 0.81 (item 12: “stool stepping”) in the study by Franchignoni et al. Construct validity has been extensively evaluated.

The total score has been shown to statistically differentiate between fallers and non-fallers and in comparison to age-matched controls. The Smallest Detectable Difference (SDD) was 2.84 points in the study by Lim et al. Another study reported 5 points. The latter study investigated people with parkinsonism with a higher mean age as compared to Lim et al. (71 years versus 62). A single BBS-assessment was then furthermore conducted by three examiners.

In this thesis, the same equipment was used in all studies (Papers I-IV). The chairs with and without armrest had a height of 45 cm. The step stool used on item 12 had a height of 17 cm. A slipper was used on item 9. On Item 8 (reaching forward) the participants were always instructed to raise both arms, but the ruler was for practical reasons not attached or held against a wall.

**UPDRS part III, and item 30 (UPDRS III)**

Motor symptoms were evaluated by using UPDRS part III, which is a recommended scale that in general has been psychometrically sound. UPDRS part III is an ordinal scale with 14 items (some are rated bilaterally) graded from 0-4. Maximum score is 108 points, and higher scores denote more severe motor symptoms.

Item 30 (postural stability) of the UPDRS part III specifically “tests the righting reflex.” It is performed by a sudden posterior displacement produced by a pull on shoulders. The examiner stands behind the patient and applies the pull manually. The patient is standing erect with eyes open and feet slightly apart and is prepared. The response to the pull is graded as follows: 0= normal, 1= retropulsion, but recovers unaided, 2= absence of postural response; would fall if not caught by examiner, 3= very unstable, tends to lose balance spontaneously, 4= unable to stand without assistance.

**Timed tests**

The standardizations of the timed tests used in Paper III are to be found within the corresponding paper. The timed tests included the ten meter walk test, Timed Up & Go (TUG), chair-stand test, one leg stance and
sharpened Romberg (tandem stance)\textsuperscript{162}. These tests have previously been found useful and reliable in people with PD\textsuperscript{105, 145, 147, 159, 161, 162}.

Posturography
Posturography in Paper III was conducted both with eyes open and closed, and without and with vibratory stimulation of the calf muscles, Figure 2.

![Figure 2. Schematic illustration of the posturographic measurement system (Paper III).](image)

The starting order of posturography (eyes open or closed) was randomized so that the participants were allocated equally. The same test order was maintained when tested both with the STN stimulation turned off and on. Spontaneous sway was recorded for 30 seconds (quiet stance) before each subject was exposed to vibratory stimulation on the calf muscles during 205 seconds. The participants were instructed to stand erect, but not at attention, on the force platform with their arms crossed over the chest. The feet were kept at an angle of about 30 degrees open to the front and with the heels approximately 3cm apart. With eyes open, the participants focused on a mark on the wall (distance 1.5 m).

FES(S) and SAFFE
Two patient-reported outcomes were used when investigating aspects related to FOF. The Swedish version of FES, FES(S),\textsuperscript{163} was used in Papers III and IV, and SAFFE\textsuperscript{97} was used in Paper IV, Table 3.
In comparison with the original version \cite{94,95}, FES(S) was extended with three items (getting in and out of bed, grooming and toileting) and the ordering of the items was changed \cite{163}. Items 1-6 constitute the Personal Activities of Daily Living (PADL) subscale. Items 8-13 constitute the Instrumental Activities of Daily Living (IADL) subscale. Item 7 is considered as an in-between item. Regarding the 13 activities, the question is phrased: How confident/sure are you that you can…without falling? Each activity is graded from 0 (not confident at all) to ten (completely confident), Table 3. When evaluated without anti-PD medication in Paper III, FES(S)-ratings were conducted with reference to their present status.

In SAFFE \cite{97} (translated into Swedish by Lundin-Olsson et al.), the respondent is asked to affirm whether the 17 activities are avoided because of a risk of falling. Three response options are used: never avoid (coded 1), sometimes avoid (coded 2), and always avoid (coded 3), Table 3. FES(S) and SAFFE were administered both before and one year after surgery in Paper IV. The questionnaires were administered when the participants were on their regular treatment, and the participants were instructed to make a general estimation when rating.

**Falls and near falls (fall diary)**
Fall diaries were used in Paper IV. Falls and near falls were registered prospectively for approximately 3 months before surgery, and during one year after surgery.

The fall diary contained the following instructions: to register every fall (F) and near fall (NF) including the time point, for definitions see Table 3. Each diary provided a short description of a fall and a near fall. It was also stated that the physical therapist was to be notified by phone as soon as possible after a fall and/or near fall. Standardized questions were then posed in order to clarify the circumstances of the fall, see Table 5. The questions were based on the work by Gray and Hildebrandt \cite{71} and Stack and Ashburn \cite{87}. When describing the activity at the time of the fall, the replies were written down and later on coded into categories.

Each participant was phoned once a month in order to rectify missing data.
Table 5. Questions in relation to falls and near falls (Paper IV)

<table>
<thead>
<tr>
<th>Questions</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did you fall and land on the ground or on a lower level? (yes/no)</td>
<td>Gray and Hildebrand</td>
</tr>
<tr>
<td>Did you nearly fall “but arrested by support from a wall, railing, other</td>
<td>Gray and Hildebrand</td>
</tr>
<tr>
<td>person, etc”? (yes/no)</td>
<td></td>
</tr>
<tr>
<td>Did you fall forward, sideways or backwards?</td>
<td></td>
</tr>
<tr>
<td>Where were you when you fell? (Indoors/outdoors-specify the location)</td>
<td>Stack and Ashburn</td>
</tr>
<tr>
<td>What were you doing or trying to do at the time?</td>
<td>Stack and Ashburn</td>
</tr>
<tr>
<td>Any outer circumstances? If so, specify</td>
<td>Gray and Hildebrand</td>
</tr>
<tr>
<td>What do you think caused you to fall?</td>
<td></td>
</tr>
<tr>
<td>How was your mobility? (good/ good, but hyperkinetic/ bad)</td>
<td>Gray and Hildebrand</td>
</tr>
<tr>
<td>Did you have any PD symptoms at the time of the fall? If so, specify.</td>
<td>Gray and Hildebrand</td>
</tr>
<tr>
<td>Did you have any other symptoms at the time of the fall?</td>
<td></td>
</tr>
<tr>
<td>How long time had passed since your last dose of anti-PD medication?</td>
<td></td>
</tr>
<tr>
<td>Did you hurt or injure yourself in any way? If so, specify.</td>
<td></td>
</tr>
<tr>
<td>Did you seek medical attention? If so, specify.</td>
<td></td>
</tr>
</tbody>
</table>

Parkinson’s disease: PD. The questions are based on the work by Gray and Hildebrandt (2000), and Stack and Ashburn (1999). If needed, examples were given in order to clarify questions 5, 6, 8 and 9. See below.

1. e.g. dark, slippery surface, walking aid, obstacle, confined space.
2. e.g. walked, turned around, got dressed or undressed, transferred from sitting to standing, did more than one task simultaneously.
3. e.g. tremor, freezing of gait.
4. e.g. felt worried/stressed/confused/tired/dizzy, an infection or pain.
5. Parkinson’s disease: PD. The questions are based on the work by Gray and Hildebrandt (2000), and Stack and Ashburn (1999). If needed, examples were given in order to clarify questions 5, 6, 8 and 9. See below.

Additional information
When evaluated without anti-PD medication, the BBS assessments preceded the UPDRS assessments in all Papers except in Paper III.

Paper I, 31 participants
Assessments were done without anti-PD medication. Before surgery, this was done on three different occasions (within six months). The BBS-scores showed no significant difference (p=0.26) between these occasions. The second test occasion had the least missing values and was therefore chosen as the baseline.
In addition to the BBS and UPDRS III, Item 30 (Postural stability) of the UPDRS part III was paid specific attention.
In an attempt to explore the intrarater reliability of the BBS, ten participants (7 men/3 women) were videotaped during testing. Their mean age was 66 years (SD 2.3), and their mean PD-duration was 15 years (SD 5.8). An equal amount of participants was filmed with and without anti-PD medication, respectively. A standardized protocol was used for the filming procedure. The videotaped performances were rated at random after two and four weeks by the physical therapist (without seeing the earlier results). The Spearman rank order correlation coefficient was 0.98 ($p<0.001$) between the two ratings. There was no significant difference between the ratings ($p>0.3$, two-tailed Wilcoxon matched-pairs signed-ranks test). At the first rating, the median score of the BBS was 46 points (min-max, 29-54). At the second rating, the median was 46 points (min-max, 28-54). Six participants attained identical points, and the other four differed at most by one point.

**Paper II, 28 participants**

The BBS-assessments were done both with and without anti-PD medications. Before surgery, the participants were assessed on two or three occasions ($p\geq0.104$) within six months prior to surgery. The second evaluation had the least missing values and was chosen as the baseline.

At the one-year follow-up, the participants were evaluated in three test conditions. Without anti-PD medication (STN stimulation turned both off and on), and with the combined treatment, i.e., anti-PD medication and STN stimulation.

At the three-year follow-up, the participants were assessed in four test conditions, i.e., both with and without anti-PD medication, and with the stimulation turned both off and on. Assessments with anti-PD medication (stimulation on and off) were for practical reasons conducted on the same day: starting with the stimulation turned on. If the patients rated their mobility as unstable, reported fluctuations or were too tired, they were however evaluated on two days ($n=7$).

**Paper III, 10 participants**

Additional demographic data were collected at admission. The participants were then asked to estimate their fall incidence during the past six months, and if they had experienced any near falls (definitions in Table 3). As a pre-assessment trial, the physical therapist assessed the participants when they felt at their best with their regular treatment, i.e. both anti-PD medication and STN stimulation (see Paper III).
All anti-PD medications were then withdrawn overnight in order to investigate the effect of STN stimulation alone. An independent person programmed the stimulation, and the start was randomized using sealed envelopes. The physical therapist was blinded to the randomization order. The assessments were performed in the following order: motor symptoms (UPDRS part III), clinical performance tests (BBS and timed tests), FES(S) and posturography.

**Paper IV, 20 participants**
Before surgery, the participants were tested with clinical assessments (UPDRS part III, BBS) and questionnaires on two occasions: prior to the decision of surgery and the week before surgery, which was approximately three months later. Before surgery, the results of the first and second test occasion did not differ statistically (p≥0.153). The second occasion was chosen as the baseline.

Before surgery, the clinical assessments were conducted both without and with anti-PD medication.

**Statistical analyses and calculations**

Non-parametric statistics were used in all studies. Group results are given as medians with the first and third quartiles (q1-q3). The Friedman test and the Wilcoxon matched-pairs signed-ranks test were used.

Two-tailed p-values <0.05 were considered statistically significant. In Papers II-IV, the p-values were presented exactly except when above 0.3 and below 0.001. In Paper II, the Friedman test was followed by the Wilcoxon matched-pairs signed-ranks test and the p-values were then corrected using the Bonferroni method. The Spearman rank order correlation coefficient (r_s) was used when investigating potential relationships.

In Paper II, 3 points was used as a cut-off score for the total BBS-score when describing a change on an individual level. This was based on the work by Lim et al. where the SDD in people with PD was 2.84 points. During posturography (Paper III), the anteroposterior and lateral body movements were recorded by the force platform and quantified by analyzing the variance of the torque induced towards the ground by the body movements. Values were obtained for five periods: quiet stance (0-30s) and from four 50-second periods during calf vibration (period 1: 30-80s; period 2: 80-130s; period 3: 130-180s; period 4: 180-230s). The torque variance values
were normalized relative to each subject’s squared height and squared mass compensating for individual variations in body constitution. For the posturography results, comparisons were done for each of the five time periods. This was conducted for anteroposterior and lateral sway, respectively, and both with eyes open and closed.

The falls (and near falls) were recalculated as number of falls/month per participant in order to compensate for any differences in follow-up time (Paper IV). The Kolmogorov-Smirnov test showed that the fall rate was not normally distributed.

Fall rate after surgery (number of falls/month per participant) was correlated with baseline characteristics: age, PD-duration, FES(S)-scores, SAFFE-scores, and the L-dopa responsiveness according to the scores on UPDRS Part III and the BBS. The latter was performed by calculating the difference score in percentage between the results without and with anti-PD medication for each participant.

New and additional data are provided about some of the measurement properties of the BBS-scores before surgery. Specifically it was assessed whether items appear to represent a common variable and the extent to which scores are reliable (i.e. free of measurement error). Whether the items appear to represent a common variable can be considered supported if corrected item-total correlations are $\geq 0.4$ \cite{165}. Score reliability (Cronbach’s alpha) was also examined, and reliability should be $\geq 0.8$ \cite{166}.

In Paper I analyses were done with GraphPad Instat version 3.00 for Windows 95, GraphPad Software Inc, San Diego, California, USA. SPSS 12.0 (Chicago IL USA) was used in Papers II and III, whereas SPSS 15.0 (Chicago IL USA) was used in Paper IV.
Results

The results are presented in relation to the used outcome measures. Missing data are explained within the Tables and in the corresponding Papers (I-IV).

**Berg balance scale**

*The effect of STN stimulation alone (Papers I, II and III)*

STN stimulation alone significantly ($p \leq 0.001$) increased the BBS-scores at the six-month follow-up (Paper I), one year after surgery (Papers I and II) and three years after surgery (Paper II), Table 6. The long-term effect was also shown in Paper III with ten participants, Table 6.

At the 3-year follow-up (Paper II), the BBS-scores increased from a median of 38 to 44 points, Table 6. Seventeen out of the 27 (63 %) participants with complete data increased their total score by at least 3 points. Three participants decreased their total score by at least 3 points. Seven participants increased or decreased their score less than 3 points.

Table 6. The scores of the Berg balance scale when investigating the effect of STN stimulation alone (Papers I, II and III)

<table>
<thead>
<tr>
<th>STN stimulation</th>
<th>turned off</th>
<th>turned on</th>
<th>turned off</th>
<th>turned on</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Paper I</strong>, $n=31$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 months, $n=24$</td>
<td>47, 37-50</td>
<td>52, 48-54</td>
<td>$p=0.001$, 3 ties</td>
<td></td>
</tr>
<tr>
<td>1 year, $n=26$</td>
<td>48, 34-51</td>
<td>50, 42-53</td>
<td>$p&lt;0.001$, 2 ties</td>
<td></td>
</tr>
<tr>
<td><strong>Paper II</strong>, $n=28$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 year, $n=26$</td>
<td>48, 37-51</td>
<td>51, 43-53</td>
<td>$p=0.001$, 1 tie</td>
<td></td>
</tr>
<tr>
<td>3 years, $n=27$</td>
<td>38, 29-48, $n=27$</td>
<td>44, 37-49</td>
<td>$p&lt;0.001$, 3 ties</td>
<td></td>
</tr>
<tr>
<td><strong>Paper III</strong>, $n=10$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean 37 months (min-max 15-70), $n=10$</td>
<td>42, 35-48</td>
<td>50, 47-52</td>
<td>$p=0.002$, no ties</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented for those with complete data in both test conditions (stimulation turned off and on). Parkinson’s disease: PD. Nucleus subthalamicus: STN.

1 At the three-year follow-up, an additional participant had data when tested with the STN stimulation turned on, but not when tested with the stimulation turned off.

*Paper I*: Missing data: 6 months ($n=7$)-2 were missed, 1 year ($n=5$)-2 due to refusal or concomitant illness, 1 due to changed target for the Deep Brain Stimulation. The remaining missing data were caused by severe fatigue, knee-pain, hip-pain or nausea. *Paper II*: Missing data: 1 year ($n=2$)-2 were missed, 3 years ($n=1$)-1 due to back-pain (stimulation turned off). *Paper III*: No missing data.
Item 11 (turning 360°) was the one item where the largest amount of participants increased their score. At twelve months, 54 % (14/26) increased their score by at least one point (Paper I).

Evolution over time (Paper II)
The participants were evaluated without any treatment, i.e. no anti-PD medication and with the STN stimulation turned off after surgery (Paper II). The one and three years’ results were compared with baseline values, Table 7. At the one-year follow-up, there was no significant (p>0.3) difference compared with the baseline values, Table 8. The BBS-scores were however significantly (p<0.001) decreased at the three-year follow-up, both in comparison with the one-year follow-up and the baseline, Table 8. Three years after surgery, 68 % (17/25) decreased their BBS-score by at least 3 points. Eight participants increased or decreased their score less than 3 points.

Combined treatment (Paper II)
Both one and three years after surgery (Papers I and II), the anti-PD medication was reduced by approximately 50 % as compared with before surgery. Three years after surgery, the mean daily dose of levodopa equivalents was reduced from 1240 mg (SD 663) to 589 mg (SD 389), Paper II. At the three-year follow-up, the combined treatment (i.e., reduced anti-PD medication + STN stimulation) further increased (p<0.001) the BBS-scores as compared with the effect of STN stimulation alone. That is, the BBS-scores increased from a median of 44 (q1-q3, 37-49) to 50 (42-52) with the combined treatment (27 had complete data).

The combined treatment effect was also investigated by comparing the BBS-scores (1 and 3 years) with the results before surgery when tested with anti-PD medication (Paper II). The Friedman test showed a close to significant difference (p=0.053), Table 7. Twenty-seven participants had complete data for a comparison between the three-year follow-up and baseline. Five out of the 27 participants had increased their total score by at least three points. Thirteen had increased or decreased their score less than 3 points. Nine participants had decreased their score by at least three points.
Table 7. Results of the Berg balance scale: without and with treatment (Paper II), n=28

<table>
<thead>
<tr>
<th></th>
<th>Without anti-PD medication, and after surgery: STN stimulation turned off</th>
<th>With anti-PD medication, and after surgery: STN stimulation turned on</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>median, q1-q3</td>
<td>median, q1-q3</td>
</tr>
<tr>
<td>Before surgery</td>
<td>n=23</td>
<td>n=25</td>
</tr>
<tr>
<td>1 year</td>
<td>n=23</td>
<td>1 year</td>
</tr>
<tr>
<td>49, 44-51</td>
<td>48, 39-51</td>
<td>52, 47-53</td>
</tr>
<tr>
<td>4 years</td>
<td>n=23</td>
<td>3 years</td>
</tr>
<tr>
<td>37, 29-49</td>
<td>p&lt;0.001</td>
<td>p=0.053</td>
</tr>
</tbody>
</table>

Friedman test, p value
n=23
n=25

Values are presented for those with complete data in all three test conditions.

Parkinson’s disease: PD. Nucleus subthalamicus: STN.

Missing data: Without anti-PD medication (n=5): Before surgery-2 were unable to perform the Berg balance scale, 1 year-2 were missed, 3 years-1 due to back-pain. With anti-PD medication (n=3): 1 year-2 were missed. An additional participant had missing data both at the 1-year follow-up and at the 3-year follow-up (infection).

Table 8. Results of the Berg balance scale: without anti-PD medication and STN stimulation turned off (Paper II), n=28

<table>
<thead>
<tr>
<th></th>
<th>Without anti-PD medication, and after surgery: STN stimulation turned off</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>median, q1-q3</td>
</tr>
<tr>
<td>Before surgery</td>
<td>n=24</td>
</tr>
<tr>
<td>1 year</td>
<td>n=24</td>
</tr>
<tr>
<td>49, 43-51</td>
<td>48, 38-51</td>
</tr>
<tr>
<td>p value</td>
<td>n=24</td>
</tr>
<tr>
<td></td>
<td>&gt;0.3</td>
</tr>
</tbody>
</table>

Before surgery versus 1-year follow-up
n=24

Before surgery versus 3-year follow-up
n=25

1-year follow-up versus 3-year follow-up
n=25

Parkinson’s disease: PD. Nucleus subthalamicus: STN. P-values are corrected for multiple comparisons (Bonferroni).

Missing data (n=4): Before surgery-2 were unable to perform the Berg balance scale (BBS), 1 year-2 were missed. Missing data (n=3): Before surgery-2 were unable to perform the BBS, 3 years-1 due to back-pain. Missing data (n=3): 1 year-2 were missed, 3 years-1 due to back-pain.
**Item 30 (“Postural stability”), UPDRS III (Paper I)**

STN stimulation alone significantly (p<0.001) improved the scores of item 30 both at 6 and 12 months after surgery. At 12 months, the median decreased from 2 (q1-q3, 1-2.3) to 1 (0-2) when the STN stimulation was turned on. The relationship between the scores on item 30 and the BBS-scores was also investigated. The correlation coefficient was calculated for each of the test conditions, and it ranged from -0.56 to -0.85 (p≤0.010), Table 9.

Table 9. Correlations between the scores of the Berg balance scale and item 30 (postural stability) of UPDRS part III (Paper I)

<table>
<thead>
<tr>
<th>Without anti-PD medication</th>
<th>Before surgery</th>
<th>6 months after surgery</th>
<th>12 months after surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>STN stimulation</td>
<td>n=29</td>
<td>n=27</td>
<td>n=26</td>
</tr>
<tr>
<td>turned off</td>
<td>-0.75</td>
<td>-0.68</td>
<td>-0.56</td>
</tr>
<tr>
<td>turned on</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The Spearman rank order correlation coefficient was used (p≤0.010, in all comparisons). Parkinson’s disease: PD. UPDRS III: motor part of the Unified Parkinson’s Disease Rating Scale. Paper I included 31 participants. Information about missing data is found within the corresponding paper. Higher scores on the Berg balance scale denote “better” balance, whereas lower scores on item 30 denote a “better” postural stability.

**Timed tests (Paper III)**

In Paper III, seven out of the ten participants reported that they had fallen during the past six months, and five of them had done so at least twice. The other three experienced near falls either every week or every month. A battery of timed tests and posturography was used when investigating the effect of STN stimulation alone. The results of all timed tests, except for sharpened Romberg, were significantly (p≤0.016) improved with the STN stimulation turned on, Table 10. That is, gait speed increased from a median of 0.91 m/s to 1.3 m/s. Both the Timed Up & Go and chair-stand test were performed faster, and one leg stance was managed for a longer time period (median: 11 s versus 26 s), Table 10.
Table 10. Timed tests: the effect of STN stimulation alone (Paper III), n=10

<table>
<thead>
<tr>
<th></th>
<th>Without anti-PD medication</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>STN stimulation</td>
</tr>
<tr>
<td><strong>Timed tests</strong></td>
<td></td>
</tr>
<tr>
<td>10 m walk test, gait speed (m/s)</td>
<td>0.91</td>
</tr>
<tr>
<td></td>
<td>0.74-1.3</td>
</tr>
<tr>
<td>Chair-stand test (s)</td>
<td>18.5</td>
</tr>
<tr>
<td></td>
<td>16.3-22.5 1</td>
</tr>
<tr>
<td>Timed Up &amp; Go (s)</td>
<td>11.0</td>
</tr>
<tr>
<td></td>
<td>11.0-18.5 2</td>
</tr>
<tr>
<td>One leg stance (s)</td>
<td>11.0</td>
</tr>
<tr>
<td></td>
<td>7.8-15.0</td>
</tr>
<tr>
<td>Sharpened Romberg (s)</td>
<td>14.0</td>
</tr>
<tr>
<td>(eyes open)</td>
<td>6.5-27.8</td>
</tr>
<tr>
<td>Sharpened Romberg (s)</td>
<td>4.5</td>
</tr>
<tr>
<td>(eyes closed)</td>
<td>2.0-12.5</td>
</tr>
</tbody>
</table>

Results are rounded as one decimal or two meaningful digits. m/s = meters per second, s = seconds. Parkinson’s disease: PD. Nucleus subthalamicus: STN. 1 (n=8). Two participants were unable to perform the Chair-stand test when the STN stimulation was turned off, but they managed the test when the stimulation was turned on: 21 s, and 17 s. 1 (n=9). One participant was unable to perform TUG unaided when the stimulation was turned off, but managed the test when the stimulation was turned on (11 s). Sharpened Romberg had an upper time limit of 60 seconds. With eyes open, this was reached by one participant with the STN stimulation turned off and by two participants with STN stimulation turned on.

**Posturography (Paper III)**

All ten participants managed to perform posturography with the STN stimulation turned on. Three participants were however unable to do so without support when it was turned off. These three participants were therefore excluded from the statistical evaluation and result presentation. The remaining seven participants showed no statistical significant differences (p values ≥0.109) in torque variance values when the STN stimulation was turned on. This applied both to quiet stance and during the different periods with vibratory stimulation, and it was irrespective of visual input and sway direction, Table 11.
Table 11. Posturographic results: torque variance values \([\text{Nm/ (kg*m)}^2]\) (Paper III), \(n=7\)

<table>
<thead>
<tr>
<th></th>
<th>STN stimulation turned off</th>
<th>STN stimulation turned on</th>
<th>p-value</th>
<th>STN stimulation turned off</th>
<th>STN stimulation turned on</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eyes Open</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Quiet stance</strong></td>
<td>0.73</td>
<td>0.74</td>
<td>&gt; 0.3</td>
<td>0.68</td>
<td>1.0</td>
<td>&gt; 0.3</td>
</tr>
<tr>
<td></td>
<td>0.54-0.80</td>
<td>0.28-0.87</td>
<td></td>
<td>0.56-1.5</td>
<td>0.45-1.1</td>
<td></td>
</tr>
<tr>
<td><strong>Period 1</strong></td>
<td>5.9</td>
<td>3.8</td>
<td>0.219</td>
<td>8.6</td>
<td>12.0</td>
<td>&gt; 0.3</td>
</tr>
<tr>
<td></td>
<td>2.8-9.1</td>
<td>1.9-7.3</td>
<td></td>
<td>6.8-10.9</td>
<td>5.5-13.0</td>
<td></td>
</tr>
<tr>
<td><strong>Period 2</strong></td>
<td>3.5</td>
<td>3.5</td>
<td>&gt; 0.3</td>
<td>6.7</td>
<td>6.7</td>
<td>&gt; 0.3</td>
</tr>
<tr>
<td></td>
<td>2.6-4.4</td>
<td>2.5-4.4</td>
<td></td>
<td>5.3-8.6</td>
<td>4.9-11.3</td>
<td></td>
</tr>
<tr>
<td><strong>Period 3</strong></td>
<td>3.3</td>
<td>4.5</td>
<td>&gt; 0.3</td>
<td>10.9</td>
<td>8.8</td>
<td>&gt; 0.3</td>
</tr>
<tr>
<td></td>
<td>2.7-5.8</td>
<td>3.2-6.4</td>
<td></td>
<td>6.3-12.5</td>
<td>6.5-13.7</td>
<td></td>
</tr>
<tr>
<td><strong>Period 4</strong></td>
<td>2.7</td>
<td>3.4</td>
<td>&gt; 0.3</td>
<td>6.8</td>
<td>7.1</td>
<td>&gt; 0.3</td>
</tr>
<tr>
<td></td>
<td>2.4-4.3</td>
<td>2.9-6.2</td>
<td></td>
<td>4.9-8.9</td>
<td>4.0-9.1</td>
<td></td>
</tr>
<tr>
<td><strong>Eyes Closed</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Quiet stance</strong></td>
<td>0.10</td>
<td>0.17</td>
<td>&gt; 0.3</td>
<td>0.36</td>
<td>0.20</td>
<td>0.109</td>
</tr>
<tr>
<td></td>
<td>0.09-1.0</td>
<td>0.04-0.44</td>
<td></td>
<td>0.12-0.72</td>
<td>0.07-0.39</td>
<td></td>
</tr>
<tr>
<td><strong>Period 1</strong></td>
<td>1.1</td>
<td>0.66</td>
<td>0.156</td>
<td>1.1</td>
<td>1.1</td>
<td>&gt; 0.3</td>
</tr>
<tr>
<td></td>
<td>0.64-5.2</td>
<td>0.48-1.4</td>
<td></td>
<td>0.87-2.7</td>
<td>0.65-1.5</td>
<td></td>
</tr>
<tr>
<td><strong>Period 2</strong></td>
<td>0.46</td>
<td>0.70</td>
<td>&gt; 0.3</td>
<td>1.2</td>
<td>0.76</td>
<td>&gt; 0.3</td>
</tr>
<tr>
<td></td>
<td>0.43-1.2</td>
<td>0.30-0.86</td>
<td></td>
<td>0.54-1.5</td>
<td>0.67-1.1</td>
<td></td>
</tr>
<tr>
<td><strong>Period 3</strong></td>
<td>0.64</td>
<td>0.52</td>
<td>&gt; 0.3</td>
<td>0.99</td>
<td>0.93</td>
<td>&gt; 0.3</td>
</tr>
<tr>
<td></td>
<td>0.26-0.96</td>
<td>0.26-0.75</td>
<td></td>
<td>0.57-1.6</td>
<td>0.77-1.2</td>
<td></td>
</tr>
<tr>
<td><strong>Period 4</strong></td>
<td>0.49</td>
<td>0.70</td>
<td>&gt; 0.3</td>
<td>1.2</td>
<td>0.73</td>
<td>&gt; 0.3</td>
</tr>
<tr>
<td></td>
<td>0.30-0.76</td>
<td>0.25-0.94</td>
<td></td>
<td>0.37-2.2</td>
<td>0.63-1.2</td>
<td></td>
</tr>
</tbody>
</table>

Torque variance values \([\text{Nm/ (kg*m)}^2]\) are given as medians and first and third quartiles. Results are rounded as one decimal or two meaningful digits (maximum of two decimals are given).

Parkinson’s disease: PD. Nucleus subthalamicus: STN.

Quiet stance: Spontaneous sway was recorded for 30 seconds. Period 1-4: Vibratory stimulation on the calf muscles. Each period lasted for 50 seconds. The vibratory stimulation increased the anteroposterior and lateral torque variance values significantly \((p \leq 0.047)\) from quiet stance to period 1 in all test conditions (STN stimulation turned off and on, eyes open and closed).

**FES(S) and SAFFE (Papers III and IV)**

The participants were evaluated after surgery and without anti-PD medication in Paper III. FES(S) was administered both when the STN stimulation was turned off and on, and the participants performed their ratings with reference to their present status. With the STN stimulation turned on, the total score of
FES(S) increased (p =0.002) in median with 54 points indicating a higher degree of fall-related self-efficacy (self-confidence).

In Paper IV, FES(S) and SAFFE were administered both before and one year after surgery. The participants performed their ratings by giving a general estimation on how they perceived it to be in their daily life, i.e. with their regular treatment. Before surgery, the median total score of FES(S) was 83 (q1-q3, 74-112) and it increased (p=0.080) after surgery to 101 (75-118). After surgery, the scores of the PADL subscale showed no significant (p>0.3) difference. The scores of the IADL subscale significantly (p=0.026) increased after surgery: from a median of 36 (q1-q3, 27-50) to 43 (32-55). Higher scores on SAFFE denote more activity avoidance due to the risk of falling. Before surgery, the median score was 25 (q1-q3, 21-30) and it significantly (p=0.007) decreased after surgery (median 22, 18-27).

Falls and near falls- fall diaries (Paper IV)

Nineteen out of the 20 participants completed the prospective follow-up with fall diaries.

Falls as well as near falls were recalculated for each participant as number per month. Falls per month was not significantly (p>0.3) different after surgery. Before surgery, the median (q1-q3) number of falls per month was 0.23 (0-0.79), whereas after surgery it was 0.25 (0-0.50). Three participants did not report any falls neither before nor after surgery.

The number of near falls per month was significantly (p=0.014) reduced after surgery. For the whole group, the median number of near falls per month was 0 both before and after surgery. The quartiles were 0-0.58 and 0-0.16, respectively. Nine participants reported no near falls neither before nor after surgery. Ten participants reported near falls before or after surgery. Before surgery, their median rate of near falls per month was 0.48 (q1-q3, 0.27-1.43), which decreased to a median of 0.14 (0.08-0.67) after surgery.

Before surgery, the follow-up period with fall diaries lasted in mean 12 weeks (SD 4.0). Ten out of the 19 (53%) participants reported falls and their median number of falls was 1.5 (q1-q3, 1-7). Five out of ten fell at least twice. During the first year after surgery, 14 out of 19 participants (74 %) reported falls. Their median number of falls was 4 (q1-q3, 2-9.3), and 12 out of the 14 fell at least twice. The highest frequency of falls was reported during the first quarter of the year during which ten out of 19 participants reported at least one
fall, Fig. 3. The Friedman test showed however no significant difference (p>0.3) when comparing the number of falls between the four quarters of the year after surgery.

Fig 3. Total number of falls (near falls not included) before surgery, and during each quarter of the year after surgery, n=19.

Bolded numbers within each bar are the number of participants that reported a fall during that specific time period. The follow-up period before surgery lasted in mean 12 weeks (SD 4.0). During the year after surgery, the Friedman test (p>0.3) showed no significant difference between the numbers of falls during the four time-periods. If the two patients that reported most falls were to be excluded, the total number of falls would instead be 14 incidents before surgery. After surgery and during the first quarter: 16 incidents, second quarter: 8 incidents, third quarter: 12 incidents and forth quarter: 13 incidents.

Two participants fell frequently. Before surgery, one participant fell 56 times and reported 90 falls during the year after surgery. The other one fell 13 times
before surgery and 64 times after surgery. If excluding these two participants, the statistical analyses were not affected.

**Relationship between fall rate after surgery and baseline characteristics (Paper IV)**
The fall rate after surgery correlated at its strongest with age before surgery ($r_s = 0.50$, $p=0.029$), and all the other correlations were below 0.40 and non-significant. The correlation coefficients with the L-dopa response before surgery (UPDRS part III and BBS scores) were $\leq 0.18$, $p>0.3$.

Twelve participants experienced at least two falls during the year after surgery. Their fall rate correlated at its strongest with age ($r_s = 0.67$, $p=0.018$) and the FES(S)-scores ($r_s = -0.67$, $p=0.017$) before surgery. The correlation with disease duration was -0.44 and non significant, and the other correlations were below $\leq 0.30$ and non-significant.

**Circumstances of falls (Paper IV)**
Both before and after surgery most falls occurred indoors ($\geq 69\%$) and most commonly in the kitchen. Most falls were connected with walking. The falls were most frequently directed forward and happened usually when the patients rated their mobility as being “bad”. An outer circumstance that might have caused the fall was specified in some of the reports, and being in a confined space was then most commonly mentioned.

**Injuries and fractures in relation to falls (Papers I, II and IV)**
In Paper I, two participants had fallen and fractured during the one-year follow-up. Both these incidents were connected with walking downstairs. During the three-year follow-up (Paper II), four falls resulted in fractures. In Paper IV, no fracture was reported during the first year after surgery (204 falls). Seventy-nine out of the 204 (39%) falls resulted in soft tissue injuries, e.g. scrapes, bruises and bumps.

**Additional results of the BBS-scores before surgery (Papers I, II and IV)**
When tested without anti-PD medication, 64 different participants had complete data (Papers I, II and IV). Reliability was 0.94. Corrected item-total correlations ranged between 0.46 (item 13) to 0.85 for items 5 and 7.

When tested with anti-PD medication, 47 participants had complete data (Papers II and IV). Reliability was 0.80, but it could only be calculated for 13
items since item 3 had zero variance. For the 13 items, corrected item-total correlations ranged between 0.39 (item 13) to 0.64 (item 10).
Discussion

It has been suggested that balance impairment can be a common side effect or adverse event after subthalamic DBS, and that those with balance disorders should be weighted carefully before selected for surgery \(^{119, 123, 133, 137}\). Previous clinical long-term studies did mainly investigate the effect on balance by using a single item of UPDRS part III, i.e. item 30 (postural stability) \(^{119, 122, 123, 127, 129}\). When evaluating the effect of an intervention, it is however of importance to also include assessments incorporating activities and participation.

The present studies are the first to prospectively investigate the effect of STN stimulation on functional balance performance, fear of falling and falls.

The effect of STN stimulation alone

One of the main reasons for choosing the BBS was its focus on functional performance \(^{12}\). The BBS has not been used in any other published study investigating the effect of STN stimulation.

The main findings of this thesis are that STN stimulation alone significantly increased the BBS scores both at short and long-term follow-up (Papers I, II and III). Statistical improvements were also shown in a majority of the timed tests and the FES(S)-scores (Paper III). The latter signifies that the participants rated themselves as having an increased fall-related self-efficacy when the STN stimulation was turned on.

Turning around is difficult for people with PD and it is associated with freezing episodes and falls \(^{52, 66, 67, 69-73}\). BBS includes a specific item investigating turning (Item 11, turning around 360 °). This item has been shown to be one of the most demanding items of the BBS for people with PD \(^{105}\). In Paper I, STN stimulation alone positively affected the scores on item 11. Timed Up & Go does also include a turn (180 degrees) and STN stimulation alone significantly improved the results of this test. An improved ability to turn may be of importance in daily life.

The posturography results showed no statistical significant difference when exploring the effect of STN stimulation alone (Paper III). This finding should however be interpreted cautiously due to the small sample size. Posturography was performed in standing and by using an external perturbation. The BBS and the majority of the used timed tests did instead mainly challenge balance
by self-generated perturbations and while moving \(^6\). The results may therefore suggest that the effect of STN stimulation is more pronounced when balance is challenged by self-generated perturbations. In daily life, perturbations to balance are usually caused by self-generated movements such as turning, bending or reaching \(^9\). Most of the falls furthermore occur during walking \(^71, 86\). In fact, only one of all the reported falls (see Paper IV) was connected with an external perturbation. The latter speaks against using solely a clinical test that challenges balance by an external perturbation.

When evaluating whether complaints of side effects are induced by STN stimulation, the stimulation ought to be turned off \(^167\). Evaluations thus need to be done both with the STN stimulation turned off and on. The present BBS-results speak against decreased functional balance performance as being a side effect induced by STN stimulation itself.

**Evolution over time in BBS-scores when tested without anti-PD medication (Paper II)**

We also investigated the evolution of functional balance performance over time. That is, the participants were evaluated without any treatment, i.e. without anti-PD medication and with the STN stimulation turned off. The reasoning for doing this was that balance impairment is coinciding with the natural progression and severity of the disease \(^63, 107, 168\). This could potentially hamper the effect of STN stimulation. In paper II, it was shown that the BBS-scores worsened over time. Although when the stimulation was turned on, the treatment was still effective three years after surgery.

STN stimulation has been suggested to have a protective effect against disease progression, but this has not been supported by the UPDRS-results in clinical long-term follow-up studies \(^119, 123-125, 127, 129\). The present BBS-results suggest that bilateral STN stimulation does not prevent a worsening of functional balance performance over time.

Ageing itself could influence when functional balance performance is evaluated prospectively. The BBS-scores have been shown to decline with increasing age which has been investigated within 10-year age cohorts \(^169, 170\). An increased age can probably not explain the decreased BBS-scores in Paper II since the follow-up period was only three years.
**Combined treatment and BBS-scores**

In daily life, a combined treatment is used. This consists of a continuous STN stimulation and a reduced dosage of anti-PD medication. Three years after surgery, the dosage was reduced by 53% which is in line with several other long-term studies\(^{119, 122, 124, 125, 128, 129}\). Despite the reduction, anti-PD medication additionally increased the BBS-scores as compared with the effect of STN stimulation alone. L-dopa has previously shown to improve the results of the BBS but the authors did not include participants treated with DBS\(^{151}\).

With the combined treatment, there was a tendency to a significant difference when scores after surgery (1 and 3 years) were compared with baseline values. The median BBS-score was lower three years after surgery as compared with prior follow-ups, and 33 % (9/27) of the participants had decreased their score by at least 3 points. This might suggest that among the remaining participants some get a beneficial effect of the combined treatment, which may compensate for a worsening of balance over time. On the other hand, the results also suggest that the effect of the combined treatment tends to wear off as functional balance performance deteriorates over time. In accordance with our findings, some long-term studies reported that the effect of the combined treatment decreased over time when using item 30 of the UPDRS\(^ {122, 127}\). Another study did not support this finding\(^ {119}\). The combined treatment effect on motor symptoms (UPDRS III) has been shown to decrease over time\(^ {122, 123, 125, 127, 128}\). Some studies did however not support the latter\(^ {119, 129}\).

**Prospective evaluation of FOF and falls (Paper IV)**

Paper IV is to my knowledge the first study that prospectively and systematically registers falls before and after subthalamic DBS. In addition, the effects on fall-related self-efficacy and activity avoidance due to the risk of falling have not previously been reported.

One year after surgery, the FES(S)-scores relating to IADL activities were statistically improved. This also applied for the SAFFE-scores. The participants thus rated themselves as having an increased fall-related self-efficacy (i.e. balance confidence) in IADL activities. The SAFFE-results indicate that fewer activities were avoided due to the risk of falling. Taken together, these results suggest a positive effect not only on activities but also on participation according to the ICF\(^ {20}\). In other words, improved fall-related self-efficacy and reduced activity avoidance due to the risk of falling may induce less limitations and restrictions.
The results cannot support any change in fall rate after surgery. This may however be caused by the limited sample size. Further and larger studies are therefore warranted in order to support or refute this finding. The rate of near falls showed a statistical significant reduction among those who experienced near falls before surgery. An exercise intervention study showed similar results in people with PD with no effect on fall rate but a significant effect on near falls 171. The reasoning for also investigating near falls was that it is common among people with PD 87, 88, and that it may further affect the person’s balance confidence and self-efficacy.

An increased awareness among the participants might be induced when using a fall diary, follow-up questions and questionnaires. This could cause changes in how one behaves. Before surgery, the questionnaires were however administered at two different time points (approximately 3 months apart) and no significant difference was found between these time points. Still, it cannot be completely ruled out that other factors besides surgery may have influenced a change in the participants’ perceptions. Schenkman et al. performed a three-year follow-up in people with PD 172. They suggested that a change in perceptions may be due to the fact that the participants had adjusted to their disease.

Studies have shown that L-dopa responsiveness on motor symptoms prior to surgery is a predictive factor for motor outcome after surgery 130, 132-134. We were therefore interested in exploring the potential relationship between baseline characteristics before surgery and the fall rate after surgery. The L-dopa response before surgery on UPDRS III and BBS-scores correlated weakly to fall rate after surgery. These results may support that falls in PD is generally, or partly, due to non-dopaminergic lesions 108. An alternative explanation is that there is a nonlinear relationship between fall rate and the measures of motor symptoms and functional balance performance. A nonlinear relationship was illustrated when investigating mobility and fall risk in frail elderly 173.

In the present study, the fall rate after surgery correlated at its strongest (r_s 0.50) with age. The positive correlation reflects that a higher age at surgery related to a higher fall rate after surgery. Some studies suggested that a younger age at surgery predicts a better motor outcome 118, 132, 135, 135, whereas other studies did not support this 130, 134, 136.
Among the recurrent fallers, fall rate after surgery correlated just as strongly with the FES(S) scores ($r_s -0.67$) as with age ($r_s 0.67$). That is, a lower fall-related self-efficacy at baseline related to a higher fall rate after surgery. These results may indicate the importance of including an outcome that incorporates the construct of self-efficacy when investigating falls in people with PD. This construct was also recommended by the Prevention of Falls Network Europe\textsuperscript{25}. The results may further suggest that fall-related self-efficacy is an important target for additional interventions such as cueing. Cues are stimuli provided either by the environment (e.g. physical therapist or caregiver) or by the individual in order to facilitate movements. Cueing training in the home environment has shown to significantly improve the FES-scores\textsuperscript{174}.

To register falls without intervening might be considered ethical unsound. All participants within Paper IV did provide their consent, and they were furthermore provided the same regular follow-ups as the other patients with STN stimulation. The strength of Paper IV, and the other studies within this thesis, would have benefited from using a control group in order to certify that potential changes over time were due to the intervention\textsuperscript{175}.

Paper IV was designed in 2002 and the design corresponds well with the recommendations published in 2005 about trials investigating falls\textsuperscript{25}. There is a consensus that prospective follow-ups are to be preferred when investigating falls, but there is a lack of consensus specifying the details of how the circumstances should be registered. In Paper IV, a reported fall was followed up by questions (telephone). Although these questions were previously used when investigating falls in people with PD, they were not validated within a Swedish sample. The decision of conducting the questions by telephone was mainly based on the assumption that this would decrease the burden for the participants. Although telephone follow-ups can induce an element of recall bias, these were conducted in median 4 days after the events. There is no guarantee that the participants would have answered the questions any sooner if using another strategy. Ashburn et al. used another strategy, and they recommended the use of follow-up questions by telephone in order to clarify the circumstances of the falls\textsuperscript{86}.

When coding the activities at the time of the fall, some participants had used general terms such as “making coffee” and “cleaning” (Paper IV). Others recalled and expressed more details, e.g. “I was bending the trunk forward”, “I was reaching forward” or “I was carrying a tray while walking”. One cannot
exclude the possibility that those using more general terms also might incorporate such movements and/or dual tasking, such as carrying an object.

_Carry over effects_

When tested without anti-PD medication, the anti-PD drugs were withdrawn overnight for 10-12 hours. All assessments with the stimulation turned off were initiated 30 minutes after switching it off. It may be questioned whether these time limits were too short to make the effects of the treatments to wear off.

A carry-over effect from STN stimulation would only influence the results when the STN stimulation is turned off. Temperli et al. showed that after turning the stimulation off, the return of PD symptoms occurred at the highest rate during the first 30 minutes. Within this time period, 75% of the worsening of motor symptoms (UPDRS III) occurred. There was however a further deterioration during several hours during which axial symptoms (including item 30, UPDRS III) required longer time than tremor, bradykinesia and rigidity. When switching the STN stimulation on, 90% of the decrease in motor symptoms was reached within 30 minutes.

If extending the time period with the STN stimulation turned off, the results in that test condition might be worse than the ones reported within this thesis. A prolonged stimulation off period would therefore probably have caused increased differences when investigating the effect of STN stimulation alone. In other words, the magnitude of change would probably be greater.

In tests without anti-PD medication, one cannot exclude the possibility of differences in carry-over effects when comparing the results before versus after surgery. This since the dosage of anti-PD medication was not kept stable throughout the study. The latter was due to clinical reasons because an unchanged medication after surgery can result in an over-treatment with severe symptoms (e.g. dystonia).

When investigating the effect of STN stimulation alone, the evaluations are done without anti-PD medication. Comparisons can however be performed differently. The results with the STN stimulation turned on versus off can either be compared at the same time point after surgery. Alternatively, the results after surgery (STN stimulation turned on) could be compared with the results before surgery. We based our comparisons purely on the results after surgery. This was done in order to minimize the risk of differences in the carry over effect of anti-PD medication as being a confounding factor. The majority
of long-term studies did instead compare the effect of STN stimulation alone with the results before surgery.\textsuperscript{119, 122-125, 128, 129} Østergaard et al. made comparisons at the same time point after surgery like we did\textsuperscript{127}. They showed that the results of item 30 were significantly improved both at one and four years after surgery although the effect decreased over time\textsuperscript{127}. In Paper I, STN stimulation alone showed a positive effect on the results of Item 30 both at six and twelve months after surgery.

The used time limits (withdrawal of anti-PD medication and stimulation) were chosen out of ethical consideration and to decrease the risk of participants dropping out. The report from the Consensus on Deep Brain Stimulation for Parkinson’s disease concluded that turning the stimulation off for 30 minutes is generally sufficient\textsuperscript{167}. Evaluations without anti-PD medication have furthermore been recommended to be performed after an overnight withdrawal\textsuperscript{178}

\textit{Evaluations with anti-PD medication}

When performing evaluations with anti-PD medication, it has been recommended to use a standardized dose of L-dopa (“defined on”\textsuperscript{178}) and preferably to use an unchanged dose after surgery\textsuperscript{177}. This was done when performing the UPDRS-assessments. The physical therapist did instead evaluate the participants when they perceived themselves to be at their best during their regular anti-PD medication. This decision was made since the “defined on” condition might not represent the “best on condition” during regular treatment at home\textsuperscript{178}.

\textit{Validity of the findings}

All included participants were recruited from the same centre and there was a predominance of male participants. PD is generally considered to be more common among men\textsuperscript{31-34, 36}. There have been a male preponderance in most of the other studies investigating STN stimulation\textsuperscript{119, 124-126, 128, 129}. Some studies reported an approximate equal amount of males and females\textsuperscript{121-123} or did not report the distribution\textsuperscript{127}. The preponderance for men may affect the generality of the findings. Comorbidity is common among people with PD and may affect their balance performance\textsuperscript{179}. In Papers I, II and IV, we consecutively included all those selected for bilateral STN stimulation. The external validity would have been hampered if excluding all those with concomitant complaints\textsuperscript{175}.  
Before surgery, several baseline evaluations were used and a practice trial was used in Paper III. This was done in order to minimize the effects of “testing” itself and that a potential intervention effect may actually be caused by a familiarity with the test\textsuperscript{175}. 

The physical therapist was only blinded to the test condition (STN stimulation turned off or on) in Paper III, and the participants were not blinded in any of the studies. When investigating the effect of STN stimulation, it is difficult to apply a double blind condition due to the magnitude of change in motor symptoms. This was stressed by Fraix et al. who conducted a double blind study including 97 participants\textsuperscript{126}. Tests were then performed on two consecutive days. Almost all guessed the stimulation condition correctly already the first day, and all did so on the second day of randomization. Blinding the participants can furthermore be hampered by the fact that they sometimes physically sense (e.g. paraesthesia) when the stimulation is turned on.

**Measures**

Criticism have been raised about how item 30 (UPDRS) is executed and scored\textsuperscript{45, 180-182}. The force and the duration of the manual pull are difficult to standardize\textsuperscript{180, 182}. The number of corrective steps backwards that should be regarded as normal are not specified\textsuperscript{180, 181}. Preparation and practice trials are used\textsuperscript{45, 180}. Unpractised responses to unpredictable disturbances are to be preferred since in daily life one does not get the possibility to practice\textsuperscript{18, 180}. Even when item 30 was performed without prior warning and practice, the results did not discriminate between people with PD and age-matched controls\textsuperscript{45}.

Timed tests were included in Paper III. These tests were chosen in order to complement the BBS and thus incorporate clinical gait tests. Another reason was to add some assessments that could be used with minimal equipment also in a home setting. One leg stance and sharpened Romberg (SR) had an upper time limit of 60 seconds. With the combined treatment (on admission day, data provided in Paper III), both the SR (eyes open) and one leg stance yielded ceiling effects above the recommendation of 15 %\textsuperscript{183}. This could speak against using these tests, but one needs to keep in mind that Paper III consisted of a selected and small sample.
When initiating the data collection in 1997, there was to my knowledge no published article that had specifically investigated the measurement properties of the BBS specifically in people with PD. Kokko et al. published an article in 1997. The vast majority of studies have been published in (or since) the midst of the first decade in 2000. In Paper I, we investigated the relationship between ratings on two occasions of the BBS (videotaped performance). This was done in an attempt to explore the intrarater reliability. We did then calculate the Spearman rank order correlation coefficient since the sample consisted of ten participants. It would have been preferable to have enlarged the study sample and to calculate the ICC. The new calculations within this framework showed that the BBS-scores had a reliability of \(\geq 0.80\), which is line with recommendations. The corrected item-total correlations were \(\geq 0.39\) which can be taken for support that the items represent a common variable.

In Paper II we used 3 points for the BBS to describe a change on an individual level. This decision was based on the work by Lim et al. Since reliability is sample dependent, the SDD should preferable have been calculated based on the data within the specific sample.

Some authors suggested that if one was to choose a single clinical assessment of balance performance when investigating people with PD, they would favour the BBS. Franchignoni et al. evaluated their participants with anti-PD medication, and they reported that item 3 of the BBS had high ceiling effects. The new and additional data provided within this framework showed that item 3 had no variability in the on condition. In Paper I, item 3 was shown to have high ceiling effects also in tests without anti-PD medication.

There is a need for further studies investigating the validity and measurement properties of the BBS in people with PD. This should include assessments both with and without anti-PD medication. Only one previous study evaluated the BBS using both standardized off and on conditions, i.e. without and with an effect of anti-PD medication. The vast majority of studies reported only BBS-scores attained in the on condition, or they did not specify in what condition the participants were evaluated. Brusse et al. described that when the testing was initiated, 68% of their participants reported that their medications were “at full strength.” Physical therapists are recommended (in clinical work and in a research setting) to evaluate people with PD both in the off and on condition.
Evaluations of the used measures need therefore to be conducted in both conditions.

The included measures within this thesis (Papers I-IV) cover all the components of the ICF. Balance control is however a complex entity to grasp and there can be additional aspects of importance that are not captured by the included measures.
Major Conclusions

- STN stimulation alone significantly increased the BBS-scores (i.e. functional balance performance) both at short and long-term follow-ups (Papers I, II and III). There are no indices that STN stimulation affects functional balance performance negatively as a side effect.

- Functional balance performance decreased over time when tested without any treatment (Paper II). Despite this, STN stimulation alone had a remaining positive effect on functional balance performance three years after surgery. Anti-PD medication further added to this effect.

- The positive effect of STN stimulation alone was also confirmed by the results of item 30, i.e. “Postural stability” (Paper I), and by the results in a majority of the timed tests (Paper III). Furthermore, the participants rated their fall-related self-efficacy as improved (Paper III). The posturography results showed no significant differences due to STN stimulation alone (Paper III), which could be caused by the limited sample size.

- The participants’ ratings relating to fear of falling showed positive effects one year after surgery (Paper IV). This indicates that the participants avoided fewer activities due to the risk of falling and that their fall-related self-efficacy had improved in more complex activities. The present results suggest a positive effect not only on activities but also on participation.

- The results in Paper IV cannot support any change in fall rate after surgery, which could however be caused by the limited sample size. Fall rate after surgery related the strongest to age before surgery (Paper IV). Among the recurrent fallers, fall rate after surgery correlated just as strongly to fall-related self-efficacy as to age before surgery. Both before and after surgery, the majority of falls were connected with walking.
Implications and future perspectives

- Functional balance performance decreased over time (Paper II), which suggests the need for additional rehabilitation in conjunction with the treatment (anti-PD medication and STN stimulation).

- Among recurrent fallers (≥2 falls during a year), a higher fall rate after surgery related to a higher age and a lower fall-related self-efficacy before surgery. This may be taken into consideration when selecting potential candidates for surgery. It may further indicate the importance of including the construct of fall-related self-efficacy when investigating falls in people with PD. Fall-related self-efficacy could also be an important target for additional interventions such as cueing.

- Both before and after surgery most falls did occur during walking which underlines the importance of gait training in people with PD.

- People with PD may prior to surgery ask how their balance might be affected after surgery. Functional balance performance is positively affected by STN stimulation itself (i.e. alone). When tested without any treatment, functional balance performance does however decrease over time. The latter may suggest a progression of the disease. Despite this, STN stimulation by itself is still effective at least three years after surgery. At long-term follow-up, the combined treatment effect does seem to wear off.

- The physical therapist assessed the participants when they subjectively felt at their best with their ordinary anti-PD medication. This was done since the “defined on” condition might not represent the “best on condition” during regular treatment at home. Furthermore, it is also of relevance since this is how a physical therapist would see the person with PD in a clinical setting and as an outpatient. It would however be of further interest to investigate if the results in this test condition mirror a “defined on” condition. The latter might be less time consuming in a research setting.
• The results cannot support any change in fall rate after surgery. This may however be caused by the limited sample size. Further and larger studies are therefore warranted in order to support or refute this finding.

• This thesis mainly focuses on functional balance performance as assessed with the Berg balance scale. None of the included measures did specifically aim at investigating dual tasking. The latter is an aspect which ought to be considered in future studies.

• It has been recommended to include an assessment of fear of falling and to use a battery of tests when investigating balance impairment in people with PD \(^4,105,153,186\). There is however no consensus of a minimal data set when doing so. Future research and international collaboration is warranted within this area, which should include both clinical tests and patient reported outcomes. There might be a potential need for adjusting existing measures and/or to develop new ones.
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