# Gait and Postural Instability in Parkinson's Disease treated with Deep Brain Stimulation of the Subthalamic Nucleus

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**PAPERS ON WICH THE THESIS IS BASED**

1. Paper I – Improved Asymmetry of Gait in Parkinson's disease with DBS: Gait and Postural Instability in Parkinson's disease Treated with Bilateral Deep Brain Stimulation in the Subthalamic Nucleus. E. L. Johnsen, P. H. Mogensen, N. Sunde and K. Østergaard. Movement Disorders 2009:24(4);590-597
2. Paper II – MRI Verified STN Stimulation Site – Gait Improvement and Clinical Outcome. E. L. Johnsen, N. Sunde, P. H. Mogensen and K. Østergaard. European Journal of Neurology, 2010:17(5);746-753
3. Paper III – STN DBS Improves Movement Amplitudes in Gait Initiation. E. L. Johnsen, P. H. Mogensen, N. Sunde and K. Østergaard. Submitted

**SUMMARY**

In late stage Parkinson's disease (PD), medical treatment may not control the symptoms adequately, and the patient may become eligible for bilateral high frequency deep brain stimulation (DBS) in the subthalamic nucleus (STN).

The effect of STN DBS on gait and postural instability is not always as predictable as the effect on clinical symptoms tremor, rigidity and bradykinesia. This may relate to the type of gait disorder or the stimulating electrode localization in the STN. We sought to evaluate the effect of STN DBS on gait performance during overground walking and gait initiation – assessed with 3D optokinetic movement analyses – and to compare the DBS effect with stimulation site localized on peri-operative MRI. The stimulation sites were grouped according to STN borders visualised on pre-operative MRI, and the active stimulation site was compared with clinical improvement and gait parameters.

STN DBS is associated with improved movement amplitude while movement duration may be unaffected by both disease and stimulation. This may imply an improvement primarily on hypokinesia including gait hypokinesia.

**INTRODUCTION**

As first described by James Parkinson in 1817, symptoms of the "shaking palsy" are "tremor in rest" and abnormally inclined posture "with a tendency to pass from walking to running pace". Today the British Brain Bank criteria of Parkinson's disease (PD) is bradykinesia and at least one of the three signs "resting tremor", rigidity and "postural instability" with unilateral presentation and progressive nature of disease (1). Bradykinesia is an emphasised sign of the disease.

MOVEMENT DISORDERS

Metabolic disturbances or structural changes in the extra pyramidal areas may trigger either a hyper- or hypokinetic movement disorder, dependent on the site of change (2;3). Parkinson's disease is a hypokinetic movement disorder caused by dopaminergic cell loss. However, pharmacological substitution with levodopa and loss of the dopaminergic neurones – and thereby the buffer capacity of levodopa – may with time induce severely disabling dyskinesias; a hyperkinetic movement disorder. At that time, surgical implantation of current leading electrodes for deep brain stimulation (DBS) may be best treatment option (4-8). Symptoms are relieved according to stimulation site, as will be discussed later. Contrary to medical treatment, DBS is continuous and the patient is relieved of symptoms throughout the day and may become able to succeed with daily activities previously rendered impossible by the disease, enhancing quality of life (9;10).

THE BASAL GANGLIA

Although different in anatomical position, in avian and mammalian brains the basal ganglia (BG) act to control learned movements through dopaminergic reward-driven feedback loops and thus provides fast processing of intended muscle activation in a subcortical and subconscious manner (11;12).

In humans and lower primates, the BG consist of the striatum comprised of the putamen and nucleus caudatus, globus pallidum interna (GPi) and externa (GPe), substantia nigra pars reticulata (SNr) and pars compacta (SNc) and nucleus subthalamicus (STN) with major ascending efferents from the output nuclei (GPi and

SNr) via the ventrolateral thalamus to the motor cortices (2;13;14) (Figure 1). Major descending and reciprocal connections between the STN and nucleus pedunculopontinus (PPN) suggest inclusion of this midbrain structure in the BG-loop definition (15). However, as the exact inference of the PPN on the cortico-BG-thalamic pathways remains uncertain, in the following we regard the PPN as a component of the mesencephalic locomotor region (MLR).

Dopamine (DA) is released from the SNc to the striatal D1 and D2 positive neurones. D1 positive GABA'ergic neurones contain substance P as part of the direct BG-pathway, activated by cortical glutamatergic descending signals and by DA from SNc. The direct pathway inhibits the output nuclei GPi and SNr, thus decreasing inhibitory GABA'ergic signals to the ventro-lateral thalamus (Figure 1A). The disinhibition is stimulated by DA resulting in increased GPi/SNr-activity when DA is lost in PD.

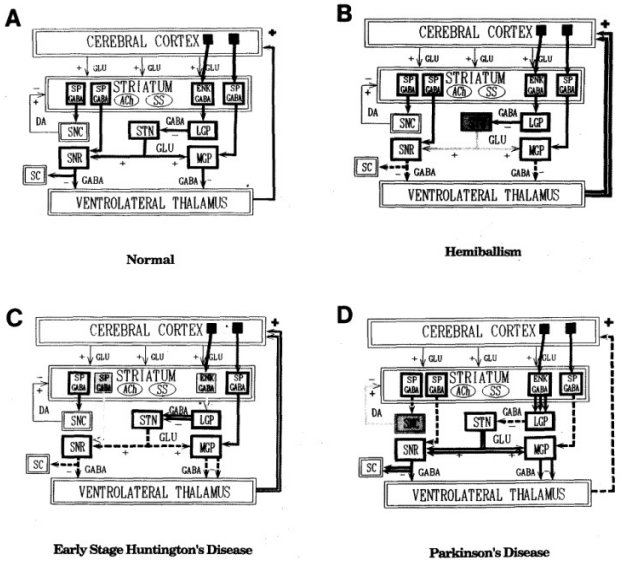



**Figure 1**
Schematic presentation of basal ganglia connectivity in normal, hyperkinetic and hypokinetic movement disorders. Structures: LGP: Globus Pallidus externa s. lateralis, MGP: Globus Pallidus interna s. medialis, SNC: Substantia Nigra pars compacta, SNR: Substantia Nigra pars reticularis, STN: Nucleus subthalamicus. Transmitters: Ach: Acetylcholine, DA: Dopamine, ENK: Enkephaline, GABA: γ-Amino-Butyric-Acid, GLU: Glutamate, SP: Substance P, SS: Somatostatin. From Albin et al. 1989 with permission by Elsevier Ltd., Oxford, UK.

D2 positive GABA'ergic neurones contain enkephaline and as part of the indirect pathway they are activated by cortical glutamatergic signals and inhibited by DA from SNc. The striatal neurones inhibit GPe, thus facilitating STN activity. DA turns down the GPe-inhibition and thereby decreases STN activity. The STN activates the GPi and SNr by glutamatergic signals and increase output nuclei inhibition on the thalamus. When DA is lost in PD, the STN is hyperactive, thus increasing inhibitory drive from the output nuclei (Figure 1D).

It is beyond the scope of this text to review all neuronal structures, pathways and substrates in relevance of the basal ganglia (16). The main theme of this thesis is STN DBS and gait and balance disturbances in PD why emphasis will be made on the STN regulation of BG output.

## THE SUBTHALAMIC NUCLEUS

### *Anatomy*

The STN originates in the cerebral peduncle from the lateral hypothalamic nucleus as a spindle shaped structure projecting

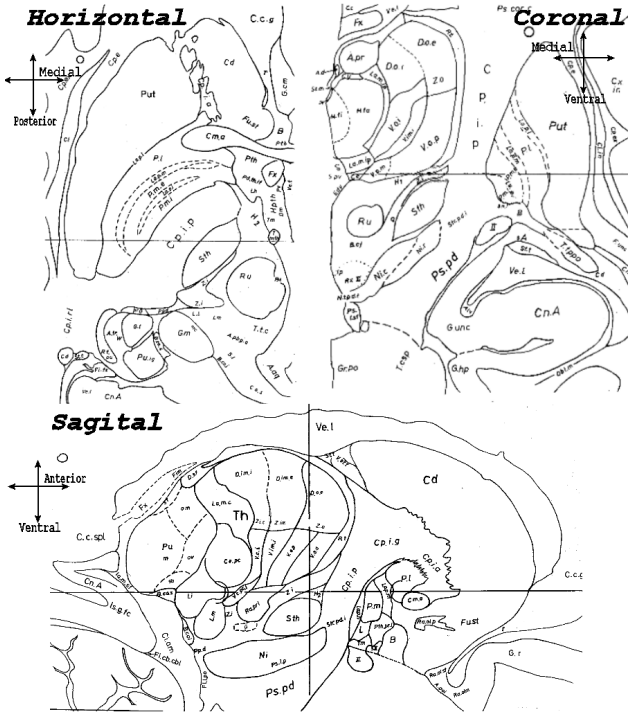



**Figure 2**
Drawing of anatomic sections of the basal ganglia in the horizontal, coronal and sagittal planes. Selected Abbreviations: II: Tractus opticus, Cd: Nucl. Caudatus, CP.i.p: Capsula Interna posterior limb, H2: Field of Forel, NI.c: Substantia Nigra pars compacta, NI.r: Substantia Nigra pars reticulate, P.l: Globus Pallidus externa s. lateralis, P.m.e./i: Globus Pallidus interna s. medialis pars externa / interna, Put: Putamen, Ru: Nucl. Ruber, Sth: Nucl. Subthalamicus, Th: Thalamus, Z.i: Zona Incerta. Adapted from Schaltenbrand and Wahren 1972 with permissions.

rostral, but may with age become more rounded or discus-shaped (17). Accordingly, the nucleus is displaced lateral and superior. Therefore the size may vary between subjects, on average assumed 6-7.5 x 9-13 x 3-4 mm (dorsal-ventral x anterior-posterior x medial-lateral)(17).

The lateral and anterior STN is separated from the GPi by the broad posterior limb of capsula interna (CI) (Figure 2). A thin layer of myelinated fibres, the H2 field of Forel, descends from the CI and separates the STN from zona incerta (ZI) and these structures cover the dorsal and rostral borders of the STN (17;18). The ZI cover the dorsal border and the upper medial STN. Caudally, the lower medial half is bordered by the fornix and comissura supramamillaris. The anterior ventral border of STN lies in close proximity to the SN: Caudally the SNc and rostrally the SNr (Figure 2) (18). Posterior, the caudal STN is separated from SNc by comissura supramamillaris and fibres descended from the CI (17).

### *STN Connections*

The main afferent input to STN is the GABA'ergic projection from GPe and the glutamatergic projections from the cerebral cortex (glutamate) although reciprocal connections with GPi, SNr and PPN also regulate the activity (2;17;19).

Efferent emitted information from the STN originates in glutamatergic neurones, predominantly reaching the BG output nuclei GPi and SNr (2;3), but also the GPe and PPN are activated by the nucleus (17).

While the GPe profusely innervate the entire nucleus, cortico-subthalamic signalling may be somatopically arranged according to the findings by Nambu et al. in monkey and Rodriguez-Oroz et

al. in man (19;20). This arrangement may act to support the STN position in three different BG pathway systems (21).

***STN Signalling***

According to the original theories of BG signalling, the STN serves as part of the indirect pathway (striatum – Gpe – STN – GPi/SNr – thalamus) in order to suppress unwanted voluntary movements, while the direct pathway (striatum – GPi – thalamus) act to disinhibit thalamocortical signalling (2;3). The hyper direct pathway acts as a shunt of cortical information (from cortex – STN – GPi/SNr, Figure 3A) to activate a general inhibition of voluntary movements (21). The inhibition is then disinhibited by the direct, slower pathway and a selected motor programme is facilitated. The indirect, slowest pathway is lastly activated in order to re-inhibit thalamocortical signals (Figure 3B) (21;22). This hypothesis on BG signalling is strongly supportive for understanding of STN and BG connections with the PPN and other brainstem structures.

Recordings of local field potentials (LFP) have increased understanding of BG connectivity. The LFP is believed to reflect synchronised dendritic currents in a group of neurones (23). Synchronisation through specific frequency bands may act as connector of BG structures with the cortex although the exact origin of oscillatory activity remains unknown (24). Synchronisation to ß-activity in the 13-30Hz-band may impair movement facilitation in both parkinsonian and healthy basal ganglia (25). Synchronisation to γ-band activity (>60Hz) is related to movement initiation and inversely related to ß-band activity (26). However, the regulation and thereby decrease of ß-activity is probably impaired in PD leading to increased power in this spectrum of activity (24;27). When levodopa is administered, ß-band activity is decreased and correlated with treatment induced improvement of motor performance (24). Indeed, recordings during levodopa-induced dyskinesias show them to be inversely related with ß-activity (28).

It should be emphasised that LFP recordings in human BGs so far only have been performed in PD patients peri-operatively and the knowledge on the ß/γ-band relationship therefore primarily rely on BG with known pathology. Also, while the ß/γ theory may contribute to the understanding of bradykinesia and akinesia in PD, different activity-bands have been suggested to play a role in PD tremor, i.e. high-frequency γ-band activity (23) but also lower frequencies around 4-10Hz, in synchrony and double-synchrony with the tremor-frequency (29;30).

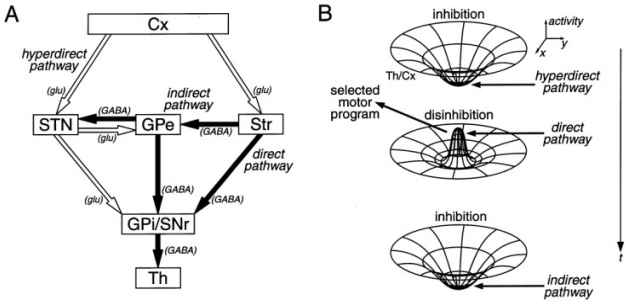



**Figure 3**

Schematic presentation of the basal ganglia hyper direct, direct and indirect pathways (A) and impact on motor program selection (B). (X,Y)-area indicate size of thalamo-cortical projection affected by activity (arbitrary units), Z-axis indicate activation type (up/positive is activation, down/negative is inhibition). Thereby i.e. a general inhibition is indicated as large area with downwards activity. Cx: cortex, GPe: Globus Pallidus externa, GPi: Globus Pallidus interna, SNr: Substantia Nigra pars reticulata, STN: Nucleus Subthalamicus, Str: Striatum, t: time, Th: Thalamus. Adapted from Nambu et al. 2002 with permission by Elsevier Ltd., Oxford, UK.

HYPOKINETIC MOVEMENT DISORDERS

Idiopathic Parkinson's disease is caused by a progressive degeneration of dopamine producing cells in the SNc. The result is disinhibition of the output nuclei and thus reduced activation of the thalamus. The progressive degeneration of dopamine producing cells in the SNc is aggravated on one hemisphere and symptoms are by definition asymmetric, most affected on the contralateral body-side (31). The asymmetric presentation is most often consistent throughout the course of the disease.

The main symptoms are probably caused by hyperactivity of inhibitory GABAergic neurons in GPi/SNr. Later in disease gait and postural symptoms develop with risk of severe falls. These symptoms may relate to the hyperactive STN and maybe to the projections from STN and GPi/SNr to nucleus pedunculopontinus (PPN) in the mesencephalon (14;32). The hyperactive STN activates the inhibitory GABA'ergic SNr projection to the PPN and probably controls muscle tone during gait and gait initiation in conjunction with the mesencephalic locomotor region (MLR) (33).

The hyper-direct pathway may not be affected by the dopaminergic deficiency (21). Cortical activation from the SMA to the STN may – hypothetically – reinforce the glutamatergic activation of GPi and SNr thus impairing activation of the desired motor-plan by increased inhibitory output in ß-band frequencies. The SNr connection increases muscle-tone which leads to akinesia and freezing of gait (FOG). This may also partly explain why FOG and other axial PD symptoms are not always responsive to dopaminergic treatment.

**HUMAN GAIT**

DEVELOPMENT OF HUMAN GAIT

Human gait deviates from most animals by the use of bipedal, plantigrade gait while most animals use quadropedal and digitigrade gait. The progression of motion originates in moving lower extremities, displacing weight towards the desired goal of movement. Development of balance during gait may be regarded as an emergence of two principles; the choice of reference and the choice of degrees-of-freedom (34). In the adulthood, we become able to use and select the articulated operation of all body parts seen in the trajectory of body centre of mass (COM) that deviates sinusoidal with motion, while the head is kept in a linear trajectory and the feet keeps hold of the COM within base of support (35;36).

INITIATION OF GAIT

The initiation of gait is the act of changing from motionless standing to steady-state locomotion (37-39). The process of gait initiation requires the sequential activation of two motor programmes; an initial postural programme to set the person off balance and a second locomotor programme to regain balance during gait. The postural programme acts through anticipatory postural adjustments (APA) prior to any gross movement is noted. The second programme consists of several sub-programmes to enable the feet to be lifted and weight transposed towards the desired goal (38). Synergy of the programmes enables the body centre of pressure (COP) and COM to perform a stable, smooth trajectory in the direction of desired path.

In stance, COP and COM is localised in the midline, just anterior to the ankle joints, reflecting the projected gravitational centre of support area. When gait is initiated, COM and COP deviates in trajectories as COM is send lateral towards the stance limb and then swung forward in order to obtain sufficient forward momentum (40). COP is initially displaced backwards and lateral

to the heel of swing limb. Then it travels contra lateral to the heel of stance limb and is then transposed forward as the stance-limb succeeds the motion (38-42).

Activation of muscles happens prior to any detection of movement in correspondence with the APA (37;43;44). The anterior shift of COM is generated by an inhibition of m. soleus and an activation of m. tibialis anterior (40;42). Loss of muscle tone in m. soleus results in a short backward sway. When m. tibialis anterior is activated, a rotational torque is build up around the ankle joint, resembling the forces of an inverted pendulum. Then, m. triceps surae is activated on the swing-limb, the heel is lifted and subsequently gait is initiated (40). Step-length and velocity of steps become the result of COM-motion and joint range of motion (ROM) (45).

STEADY-STATE GAIT

The neural control of balance during gait is highly different from the motor programmes controlling gait initiation or stance (36). During walking the COM is projected forward, ahead of support area indicated by the foot positioning and thereby creates a continuum of imbalance (46). Falling is effectively alleviated by limb swing ahead of COM, coordinated through hip-, knee- and ankle-movements (36).

Once the body is in motion, its own kinetic forces keep it moving. The coordination of muscle-activation is located on spinal level in the central pattern generators (CPG) (47). Accelerating muscle action is acquired during swing phase when the m. iliopsoas and m. quadriceps femoris bring the limb forward to maintain continuity of the gait cycle. Once the limb is in stance phase, most muscles exert controlling forces on the limb by decelerating movement of the limb segments to stabilise the joints (48).

CPG activation is not sufficient for weight support; it probably serves to withhold rhythm during walking (49). Descending cortico- and bulbo-spinal tracts acts to stabilize and regulate joint movements during the gait, active during any phase of gait (49). The CPGs ascend information to cerebellum regarding rhythm. It is unclear whether the cerebellum exerts maintenance or regulation of the rhythm. Tractus vestibulo-spinalis stabilises muscles to secure balance in stance phase. The rubro- and reticulo-spinal pathways integrate cerebellar information on limb-length and –position and are active during swing-phase. Tractus tecto-spinalis integrates sensory information on the sub-conscious level to regulate movements according to environmental threats, i.e. visual or auditory information. Tractus cortico-spinalis (CST) from the primary motor cortex is responsible for movement amplitude; when passing an obstacle the intensity but not the phase of the CST signalling increases (49). In the same way, step length may be regulated by motor activation of the pyramidal tract.

Thus, the stride variability in overground walking is maintained on spinal and brainstem level while the movement amplitudes continue to be planned by the BG acting on motor cortex' programming.

**GAIT AND BALANCE IN PARKINSON'S DISEASE**

NEURAL BASIS FOR GAIT HYPOKINESIA IN PD

Increased inhibition of the thalamo-cortical fibres by hyperactive GPi may explain the disorganised movements with especially hypokinesia. Co-activation of postural muscles may relate to the descending brainstem pathways and may explain why not all PD symptoms are treatable with levodopa (50). It is suggested that excessive GABA'ergic inhibitory output from the ascending BG connections decreases amplitude of motion while the GABA'ergic output to the brainstem area hyper-inhibit muscle tone and thereby rhythm generation in PD (33).

Prior to any movement of the limbs or body weight, the bereitshaft potential (BP) (the readiness potential) is registered as a bilateral early BP and a late BP, ipsilateral to the movement (51). The early BP originates in the supplementary motor cortex area (SMA) and is impaired in both timing and amplitude in PD (52). The early BP may reflect cortical activation correspondent with APA-initiation (53;54), while the late BP is normal in PD and may reflect conscious preparation of the movement originated in the primary motor cortex (51).

Functional neuroimaging of PD patients and healthy subjects suggest an impaired recruitment of both cortical and subcortical motor regions regulating kinematic parameters of movements (55;56). PD patients reduce movement amplitudes to synchronize movements according to demand while the temporal errors are comparable with healthy subjects (56). Studies have shown that temporal differences between PD and healthy subjects are minimal, when the followed target is predictable (56;57).

According to Fitt's law of movement-precision requirements, movement time increases with the level of difficulty (58) but a large movement is still required to take longer time than small movements. In PD, patients may manage complex movements by breaking them down to pieces by aid of vision as can be observed in micrographic PD handwriting (57). Automatic movements, like anticipative postural adjustments, that should take part in sequential movements however, may not always be dissected into visually guidable chunks and is therefore impaired in PD (57).

Deactivation of the primary motor cortex and supplementary motor area (SMA) and increased action selection and visuosensory feedback correlate with decreased movement velocity in PD (56). It could be suspected that the activated areas contribute to a pre-programming of movements why the timing and duration of motion remain intact in PD to compensate hypokinetic movements.

GAIT IMPAIRMENT IN PD

Overground walking in PD is characterised by short steps with festination and compromised limb swing, compensated by propulsion. Compared with healthy controls, gait is slower because of shorter steps (59-61). EMG-patterns of lower limb muscles in PD patients show step execution and postural stability are affected due to simultaneous activation of agonistic and antagonistic postural muscles (62).

Increased knee flexion and hypokinetic ankle movements impair the foot to lift adequately from the ground compared to healthy elderly. Stride length becomes reduced, often causing a propulsive gait as the centre of mass (COM) is send forward, often even ahead of the supporting limb (59;61). Indeed, this hypokinetic ankle joint may result in digitigrade gait comparable to what is seen in children (63) and due to poor balance result in or resemble festinative running (37;39).

Symmetry of PD gait has been evaluated by comparing the velocities of two successive steps using the fastest step as denominator. In healthy controls two successive steps have a symmetry factor of "1". In PD patients the index is "<1" indicating one stride to be slower than the other and thus indicating asymmetry not only in cardinal symptoms but also in PD gait (59). No correlation has been shown comparing gait symmetry with clinical UPDRS-symmetry, but asymmetric gait has been related to FOG and fear of falling (64;65) and to impaired initiation of gait (66).

Therefore, the study of effect by any treatment for postural instability and gait disability (PIGD) should focus on movement

**Table 1**

**Historical and present targets for deep brain stimulation. Table build on literature-search using embase and medline query ["deep brain stimulation" and target and *disorder*].**

| Disorder | Target |
|---|---|
| Parkinson's disease | Nucl. Subthalamicus (dorsolateral part)<br>Globus pallidus interna (posteroventral part)<br>Nucl. Ventralis intermedius of thalamus<br>Nucl. Pedunculopontinus |
| Essential tremor | Nucl. Subthalamicus (dorsolateral part)<br>Nucl. Ventrali intermedius of thalamus<br>Nucl. Ventralis oralis posterior of thalamus<br>Zona incerta<br>Posterior subthalamic area |
| Dystonia | Globus pallidus interna (posteroventral part)<br>Nucl. Ventrali intermedius of thalamus |
| Pain | Periaqueductal grey |
| Epilepsy | Nucl. Subthalamicus<br>Nucl. Caudatus<br>Hippocampus<br>Cerebellum<br>Nucl. Centromedianus of thalamus<br>Nucl. Anterior on thalamus |
| Cluster headache | Posterior hypothalamus |
| Depression | The subgenual cingulated cortex<br>Capsula interna<br>Globus pallidus interna<br>Nucl. Accumbens |
| Obsessive-compulsive disorder | Capsula interna<br>Ventral striatum<br>Nucl. Accumbens |
| Tourette's syndrome | Nucl. Centromedianus of thalamus<br>Capsula interna<br>Globus pallidus interna |
| Hypertension (experimental) | Periaqueductal grey |
| Obesity (experimental and hypothetical) | Hypothalamus<br>Nucl. Accumbens |

amplitudes. Also, the symmetry of movements may be impaired in PD and should be emphasised in analyses of balance during gait.

**DEEP BRAIN STIMULATION**

Deep brain stimulation (DBS) is the implantation of current leading electrodes into the deep structures of the brain, i.e. the basal ganglia structures, for continuous deliverance of high frequency and in case of gait and balance disturbances sometimes lowers frequency stimulation (67). The treatment is now offered to a variety of psychiatric and neurological brain diseases, chronic pain and experimentally for obesity and hypertension (Table 1).

While lesion in the normal subthalamic area can induce ballism (Figure 1B), STN DBS improves PD symptoms but dyskinesia can be provoked (68-70). In STN DBS reduction of dyskinesia is probably secondary to reduction of PD medication. Other targets for high frequency stimulation (HFS) of clinical relevance for PD are nucleus ventralis intermedius (ViM) of thalamus (decreasing tremor) (71), the output nucleus GPi (improving PD motor fluctuations and dyskinesias but no significant reduction of PD medication) (72;73) and suggestively the SNr (supposedly reducing gait disability) (74). Recently, the PPN has been introduced as a potential target for low frequency stimulation (LFS) in frequencies <60 Hz to treat gait and balance disturbances in PD (75;76).

CLINICAL OUTCOME

Follow-up studies have documented the clinical benefits of STN DBS are substantial and persistent after several years of treatment (6;77-81) (Figure 4). However, although treatment is targeted the basal ganglia directly, the course of disease is still progressive (Figure 4). This may explain the often debilitating symptoms with gait deterioration (80). Reported adverse events to surgery and stimulation such as dysarthria and eyelid apraxia are probably related to stimulation site (9). Furthermore, clinical benefit may depend on age at operation (82;83).

STN DBS ACTION METHOD

Concerning the exact mechanism of DBS action this is unresolved and a matter of intense debate. Suggestions have implied differential effects when stimulating electrode is in grey vs. white matter but also dependent on distance from neuronal cell-body to stimulation electrode. Also, contradictory findings propose both excitatory and inhibitory effects of HFS on BG signalling.

Four general hypotheses may be summarised regarding DBS action methods: 1) depolarisation blockade, 2) synaptic inhibition, 3) synaptic depression and 4) modulation of pathological network activity (84). The interpretation of results obtained during the search for the action method, however, may be biased by different philosophies on the DBS effect; a) induction of a functional, reversible ablation versus b) stimulation and modification of neural networks (84).

Overall, the DBS effect on output from local cells is dependent on the frequency (LFS or HFS) and positioning of the neuron with respect to the electrode (84). Different activation thresholds exist in neurons and axons. Therefore, local cells close to the stimulating electrode may be both directly and indirectly affected through activation of the cell body (direct) and by activation of afferent inputs (indirect) while neurons located more distant may be only indirectly affected. However, the anisotropy of brain tissue may induce wide-spread effects of the stimulation which cannot be accounted for when trying to determine the exact stimulation site. Therefore volume of tissue activated by both LFS and HFS may differ in white and grey matter (85).

When applying HFS stimulation directly into the STN, the frequency pattern may resemble γ-band activity over ß-band activity, thus enabling kinesis (26). This is contrary to LFS that is antikinetic when applied to the STN, probably resembling ß-activity (26). This may increase the understanding of contradictory findings of neuronal activity in the stimulated targets (84). Following STN stimulation in a non-human primate, efferent firing to the GPi and GPe was increased (86). Also, microdialysis-studies showed increased extracellular glutamate in rat-BG output nuclei (SNr and the entopeduncular nucleus). Increases of neurotransmitters have been found to correlate with stimulation frequencies from 60Hz and above (87), also suggesting that DBS >60Hz induces ß-band activity decrease and maybe induction of synchronisation to γ-band activity.

Recent studies suggest that the aforementioned hypotheses should be regarded as different aspects of the same process while the latter philosophic approach seems most reasonable. This is further emphasised by the results in parkinsonian rats where optical HFS of the STN focused only onto the subthalamo-primary motor cortex-projection system improved movement length

while 20Hz LFS (in the ß-band frequency range) had no effect on akinesia (88). It has also been suggested that spinal-cord stimulation could improve PD symptoms by action of the thalamo-cortical signals. While this has been proven in rats (89), human spinal-cord stimulation failed to improve PD bradykinesia (90).

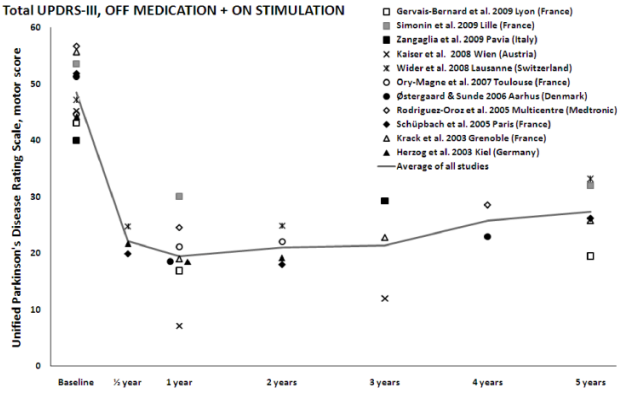



**Figure 4**
Plot of documented clinical benefit by STN DBS after one year or more. Plot indicates study-average of baseline UPDRS-III off medication and follow-up UPDRS-III score off medication, on stimulation.

## STUDY AIMS

SURGICAL EFFICACY ON GAIT PERFORMANCE

A meta-analysis from 2004 documented that, the effect of DBS on postural instability and gait disability (PIGD) resembles the best performance on levodopa-treatment (91). It was also documented that PIGD may worsen after electrode implantation as a possible side-effect to stimulation. Follow-up studies have also documented this un-attractable effect of treatment (5;6). To reveal deeper insights to gait disability and performance, examination of sub-elements of gait can be assessed by quantitative gait analyses. STN DBS improvement of "gait performance" can thereby be quantified.

We aimed to elucidate the effect of STN DBS on gait performance during overground walking and gait initiation using quantitative gait analyses. Furthermore, the thesis includes a meta-analysis of our and others' findings in order to hypothesize on the possible effects of STN DBS on neuronal systems controlling motor performance.

THE MOST OPTIMAL STIMULATION SITE

Speculations can be made on the actual inference of stimulation in deep structures closely related with other functional brain areas. Therefore, knowledge on the active stimulation site may become crucial for prediction of clinical outcome. Also, stimulation induced side-effects e.g. dysarthria is known dependent on stimulation position (92).

The STN is targeted using different visualisation modalities. The standard coordinates with respect to anterior and posterior commissural midpoint (AC, PC) place the centre of STN approximately 12 mm lateral, 2.5 mm posterior and 4 mm inferior (7). The location of electrodes may be verified by peri-operative MRI, prior to the implantation of the pulse generator and the clinical outcome be related to the actual stimulation site.

While recent documentation has proven this relationship regarding symptoms tremor, rigidity and bradykinesia, the relationship has not been documented regarding gait improvement.

We aimed to compare the effects of STN DBS on gait performance with stimulation site in the STN. Also, the thesis will include a review of the most efficient stimulation site reported by us and others.

## METHODS

In the following, methods used are presented in abbreviated form. For further details on selections of specific parameters of interest please, refer to the papers.

PARTICIPANTS

***Study I: Effect of STN DBS on Overground Walking***

Twenty-one patients participating in a contemporary study who had bilateral STN DBS performed between November 2002 and November 2004 with at least 25% known improvement of the UPDRS-III at the time of 6 months evaluation postoperative were potentially candidates for participation. Patients were excluded if they were demented or had other concurrent affection of gait performance, i.e. arthrosis or stroke. 16 patients were contacted by letter. Gait analyses were performed at least 12 months post-surgery.

Twelve healthy controls, matched on age and gender, were selected from our background population, age 56 to 65 years, at the Laboratory of Gait Analyses, Hammel Neurocentre. Patients gave written informed consent and the protocol was approved by the local ethical committee.

***Study II: Impact of Active Stimulation Site on Gait Improvement***

Twenty-four patients had bilateral implantation of STN DBS electrodes performed between February 2003 and March 2007 on basis of the same surgical protocol with preoperative planning and peri-operative verification on 1.5 Tesla MRI. Patients whose peri-operative MRIs were present and who had had 12 months UPDRS-III evaluation were enrolled in the study.

***Study III: Effect of STN DBS on Gait Initiation***

Patients from study I also completed the assessment protocol for gait initiation during the same visit. Due to severe drop-out in study I, patient-files of additional thirteen patients, treated with bilateral STN DBS until September 2007, were scrutinised on basis of the criteria mentioned above and eligible patients were contacted by letter.

As the gait initiation assessment-protocol is not standard at our gait laboratory, ten healthy controls were recruited from local community, matched on age and fulfilled the same exclusion criteria as patients with special emphasis on other concurrent disorders of gait performance, i.e. arthrosis or severe obesity.

QUANTITATIVE GAIT ANALYSES

Gait analyses were performed at the Gait Laboratory, Hammel Neurocentre, using a Vicon 612 gait analysis system (Oxford Metrics, Oxford, UK). Gait analyses were performed according to the PlugInGait model (93;94) with eight infrared cameras and two steady digital cameras recording 39 retro-reflective markers on the subject. Temporal resolution of infra-red cameras was 100Hz, steady digital cameras 25Hz.

Full body-marker set-up was used to calculate COM position, step lengths and velocities and joint kinematics. Joint kinetics were calculated with use of an AMTI force-plate embedded in the floor (Advanced Medical Technology, Inc., Watertown, MA, USA).

Patients were asked not to take anti-PD medication at least 12 hours before gait assessment and randomised to do first test ON or OFF STN DBS (95). Gait assessment was performed at least three hours after change of stimulation condition (96).

***Protocol for Assessment of Overground Walking (Study I)***

Patients walked bare-footed in their own preferred pace on a one meter wide and 10 meter long walkway. No indication was made about foot positioning. Patients were asked to walk until

there had been three full hits on the force plate by each foot, if they were able. The investigated trial was selected by comparing average velocity of the posterior-superior-iliac marker in each trial. The left and right trials closest to mean value was chosen.

The middle-gait stride was chosen for further evaluation and standardised to standard gait cycle (Figure 5).

For further details on parameter-selection, please refer to the study I-paper.

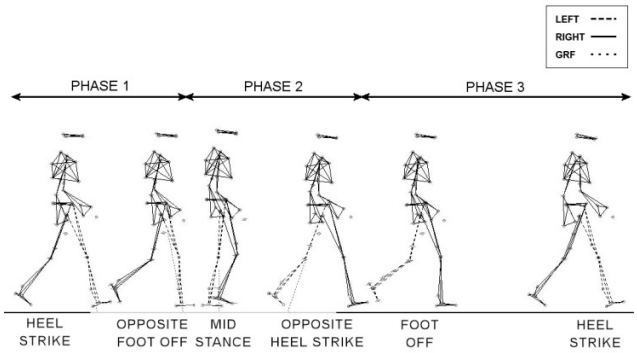



**Figure 5**
Standard gait cycle with indication of specific temporal events. Adapted from Johnsen et al. 2009, with permission from John Wiley & Sons Ltd., West Sussex, UK.

LOCALISATION OF THE ACTIVE STIMULATION SITE (STUDY II)

All localisation analyses were performed retrospective after implantation, blinded to clinical outcome.

The STN was localised on preoperative T2-weighted MRI using the Surgiplan 2.0 software. The nucleus was carefully marked and distinguished from surrounding structures by comparing the axial, sagittal and coronal views of the scan. The STN area was defined as the hyper-intense formation dorso-lateral to the substantia nigra (coronal view).

Peri-operative MRI was fused onto the existing preoperative MRI with the STN marked, using the Surgiplan 2.0 software, based on land-mark fusion of grey-scale areas on the MRI.

Each set of MRI were aligned parallel to the axis of the permanent electrode trajectory. Centre of artefact bottom was regarded as "contact 0" (97). The active contact at 12 months follow-up was noted from patient files and located on MRI by increasing the distance from "contact 0" with two millimetres per inactive contact in direction of the electrode trajectory. Position of the active contact was categorised as either in the dorsal half or in the ventral half, or in medial or lateral relation hereto, as depicted in Figure 6. Coordinates relative to mid-commissural point were calculated. For further details on parameter-selection, please refer to the study II-paper in appendix.

PROTOCOL FOR ASSESSMENT OF GAIT INITIATION (STUDY III)

Each subject was instructed to stand one-two meters behind the embedded force-plate, walk into the force-plate area on an auditory signal and stand with both feet, regaining postural balance. When a visual cue was given (random after 10-15 seconds), subject walked to the end of the room (5 meters) with self-selected initial swing-limb and pace. No indication was made about foot positioning. Average velocity of the swing-limb posterior-superior-iliac marker during gait was calculated for up till three trials; the trial closest to average velocity was chosen for analysis. When only two trials were made, the fastest trail was selected to compensate possible influence of e.g. distraction or fatigue.

For further details on parameter-selection, please refer to the study III-paper in appendix.

META-ANALYSIS OF QUANTITATIVE GAIT ANALYSES AND PD DBS

EMBASE and MEDLINE was searched using the string ["deep brain stimulation" AND "Parkinson disease" AND ("Subthalamic Nucleus" OR "Globus Pallidum" OR "Pedunculopontine Nucleus") AND Gait]. Last search performed end of April 2010. Secondarily, relevant reference-lists were reviewed.

Study inclusion-criteria were: Quantitative gait analyses performed on idiopathic PD patients treated with DBS in either GPi or STN. Exclusion criteria were: failed comparison of "off medication, off stimulation" with "off medication, on stimulation", failed documentation of parameter average and standard deviations in both conditions.

Outcome measures were: total UPDRS-III, UPDRS-III item 29; "Gait" and gait velocity, cadence, stride or step length, stride or step duration and double support. Studies were not excluded if they did not present all outcomes.

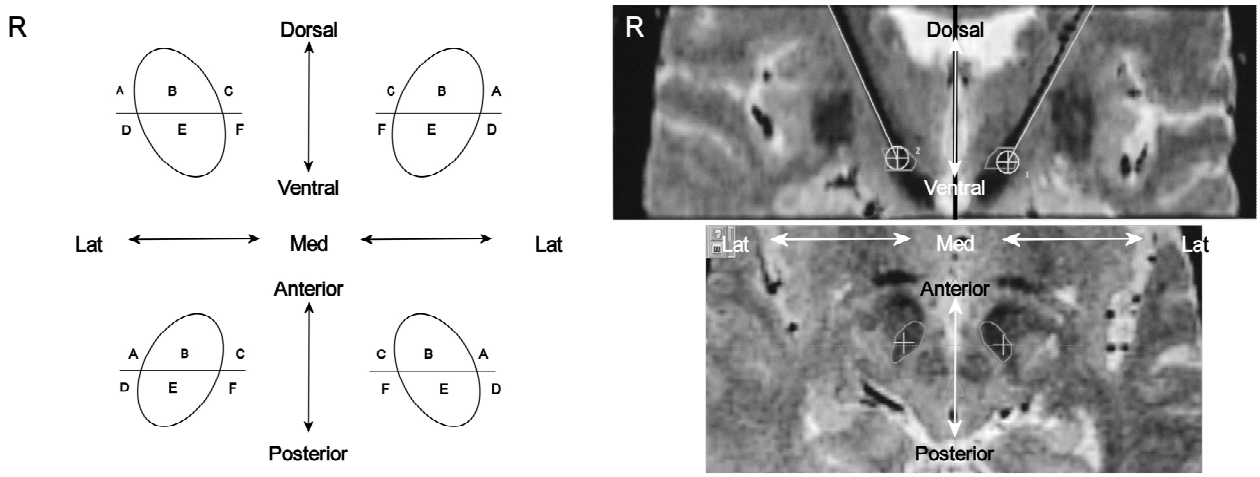



**Figure 6**
The STN was localised on coronal and horizontal MRI (right). Stimulation site was categorised according to nucleus borders (left). Adapted from Johnsen et al. 2010, with permission from John Wiley & Sons Ltd., West Sussex, UK.

REVIEW OF MOST OPTIMAL STIMULATION SITE

EMBASE and MEDLINE was systematically searched using the string ["deep brain stimulation" AND "Parkinson disease" AND "Subthalamic Nucleus" AND contact position], latest search end April 2010. Secondarily, reference-lists of included studies were reviewed. Study inclusion-criteria were: Presentation of outcome on UPDRS-III, presentation of coordinates of the active contacts relative to mid-AC/PC and documentation that in each included patient, the most optimal stimulation site had been searched.

STATISTICS

Change in patient baseline characteristics were analysed as paired data using Student's T assuming equal variances and normal distribution. Healthy controls demographic data, e.g. height and age, were compared with patients' data using chi-square or Student's T where applicable. Level of significance in all tests was p=0.05. Healthy controls were used as reference-group when assessing improvement or impairment by STN DBS of a specific parameter.

***Study I: Effect of STN DBS on Overground Walking***

Gait parameters and UPDRS-III scores OFF DBS were compared with ON DBS, analysed as paired data assuming equal variances using Student's T. When comparing body sides, mean difference of the same stimulation status was analysed with a Z-test. The effect of DBS on body-side differences was analysed as paired data using Student's T. Gait parameters in PD patients in both DBS-states were compared with healthy controls, analysed as paired data assuming unequal variances due to different study-sizes using Student's T. Level of significance in all tests was p=0.05.

***Study II: Impact of Active Stimulation Site on Gait Improvement***

Evaluation of influence by active stimulation site on clinical outcome was analysed with respect to the contra lateral body side. When the parameter of interest applied to midline symptoms, bilateral electrodes were analysed, e.g. total and axial UPDRS-III and gait velocity.

In respect of data distribution based on QQ-plots and variance-ratio F-test, only non-parametric tests were performed and results are given as medians and (ranges). Clinical benefit on motor symptoms and gait improvement was analysed as paired data with Wilcoxon signed rank. Grouped anatomical stimulation areas were compared with clinical outcome and gait performance and analysed with the non-parametric Kruskal-Wallis rank test and effect within groups was analysed with the Wilcoxon-Mann-Whitney ranksum test. Level of significance in all tests was p=0.05.

***Study III: Effect of STN DBS on Gait Initiation***

Data distribution was evaluated with QQ-plots and variance-ratio F-test used for assessing equal variances. Initiation parameters were analysed as paired data using Student's T where normal-distribution could be assumed and variances found comparable. If normal-distribution could not be assumed or variances found statistically different, data were analysed with non-parametric Kruskal-Wallis rank test. Linear regression was used to test for correlation of two parameters in the same stimulation-status. Level of significance in all tests was p=0.05.

***Meta-analysis***

Meta-analyses were based on a Random Effect-model approach assuming normal distribution of data using Review Manager 5 software (98).

Analyses were stratified to stimulation site. Level of significance in all tests p=0.05.

**RESULTS WITH COMMENTS**

Results are presented in an abbreviated form with emphasis on positive findings. Please see the papers for further details on results.

PATIENTS

Patient characteristics are presented in detail in appendix A.

Of the thirty-four possible participants, two had died before studies were initiated and two were regarded too demented to be enrolled. Four patients had musculoskeletal affection of gait performance, i.e. hip arthrosis. One had had a frontal stroke. One did not respond to inquiry and four did not want to participate when stimulation should be turned off. Summary of patient characteristics in the individual studies are presented in the papers.

***Postoperative Change, all enrolled patients***

Median age at implantation was 62 years (range 40;69) and average PD-duration was 13.9 years(±4.5).

Daily levodopa equivalent dose was significantly reduced 12 months after implantation, average decrease 383(±344) LDEQ correspondent to 33%(±29%), p<0.05. On average, total UPDRS-III was significantly reduced by 27.6(±8.6) points, correspondent to 62%(±15), p<0.05.

***Comments***

Reduction of medication has been a measure of surgical efficacy regarding STN DBS. However, due to different therapeutic strategies among individual treatment centres, this evaluation may not necessarily reflect the actual stimulation effect as much as the treatment-philosophy of the centre.

Four patients were unable to walk OFF STN DBS on basis of impaired postural reflexes, UPDRS-III item 30 "unable to stand without assistance". Presented gait analyses are based on the remaining patients who were capable of walking OFF DBS. Therefore, we cannot rule out a "regression-towards-the-mean", i.e. average gait velocity of all patients OFF DBS is lower when including those unable to walk (4 patients with velocity = 0m/s) and the difference induced by STN DBS is therefore larger than presented. However, post-hoc power-analyses have indicated fair to strong study-power in all parameters showing either good or no improvement.

STUDY I: EFFECT OF STN DBS ON OVERGROUND WALKING

Gait velocity and stride lengths were improved ON DBS. Temporal parameters of cadence and stride time did not differ between PD and controls or between stimulation statuses. Double support phase was prolonged OFF DBS compared with control group and improved ON DBS (study I-paper, table 2).

OFF stimulation, PD patients placed one heel closer to COM at heel strike than on the other body side. The same asymmetry was seen in all related spatial parameters of gait performance, i.e. step length and joint moments. This was not observed in healthy controls. Length between heel marker and COM at heel-strike (HEE-COM) therefore define the most or least affected body side (MAS resp. LAS). STN DBS equalised and increased all distances although they were still impaired to healthy controls (Figure 7 and study I-paper, table 2).

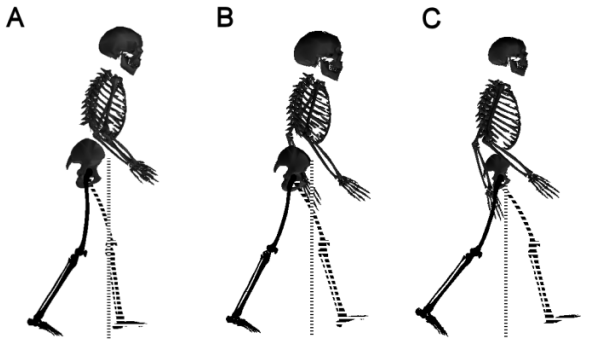



**Figure 7**
Placement of the heel relative to COM (vertical line) at MAS heel-strike (front leg) OFF STN DBS (A), same patient ON STN DBS (B) and left foot of a healthy control (C).

Step time on LAS was comparable in PD patients at all times and healthy controls. Timing of events "opposite foot-off" and "opposite heel-strike" were therefore asymmetric OFF DBS with impairment on the MAS. No asymmetry in events was observed ON DBS.

Range of motion was improved by STN DBS on major lower extremity joints (study I-paper, table 3).

OFF DBS, the knee joint moments and power generated at "opposite foot off" were asymmetric reflecting unequal loading response (study I-paper, table 3). The ankle joint dorsal flexion was asymmetric OFF DBS prior to push-off (Figure 8). No asymmetry was seen ON DBS.

***Comments***

DBS facilitates larger steps taken in the same amount of time in overground walking. Thereby gait velocity is increased but cadence unaffected. Main abnormality in PD overground gait is the abnormality in the stride length/cadence relation (99). Previous studies on self-paced overground walking have calculated the contributions of amplitude and cadence to velocity-increase and described the non-linear relationship in improvements (100-102). Our findings are supportive that STN DBS improves hypokinesia without changing movement duration.

Our analyses of symmetry are based on asymmetry in the HEE-COM parameter. Other studies have used step-time of left and right legs to describe symmetry but first of all, they did not find asymmetry and secondly it therefore was not affected by DBS (100;103). As temporal parameters may not be affected by PD, it may not be the optimal common denominator of gait impairment. Therefore, we used the HEE-COM length although it did not correlate with UPDRS-III asymmetry, but was consistent with all other spatial asymmetric parameters.

Only few other studies have investigated changes in the lower limbs' kinematics and kinetics induced by STN DBS (101;102;104). Although their results are comparable to the values in our study, interpretation differ regarding especially the ankle joint, i.e. suggesting the ankle "…is the most affected joint in PD, [but] least improved by DBS" (104). Rather, our results indicate an improvement in ankle push-off that leads to increased swing amplitude

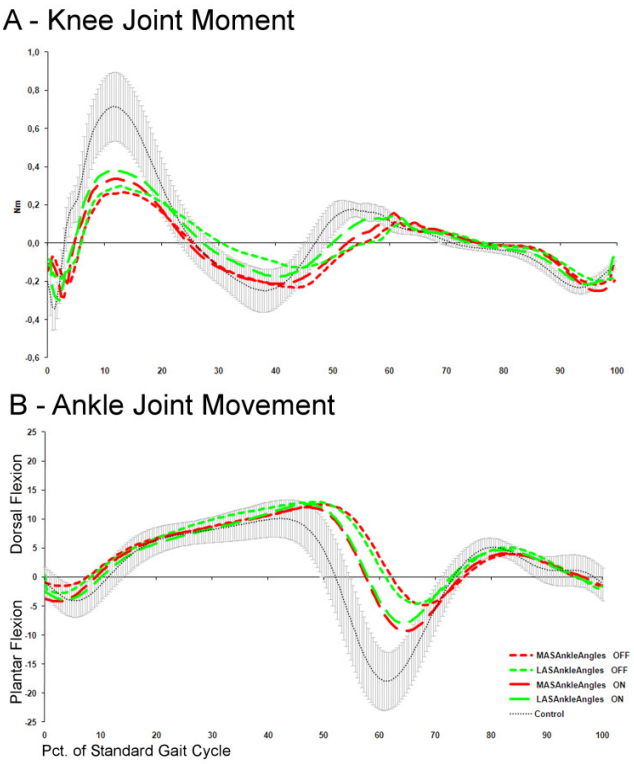



**Figure 8**
Knee joint momentum (A) and ankle joint motion (B) during gait cycle, OFF and ON DBS and in healthy controls.

(step length) and therefore increasing knee joint momentum. This improves balance during gait so that reduced inclination of the upper-body keeps COM within base of support (HEE-COM length is increased).

STUDY II: IMPACT OF ACTIVE STIMULATION SITE ON GAIT IMPROVEMENT

Target coordinates and position of the active contact was localised on peri-operative MRI and plotted (Figure 9). Average preoperative target coordinates for positioning of the second lowest contact ("contact 1" on the electrode) was Xt=12.0(±0.7); Yt=-2.0(±1.3); Zt=-4.2(±0.5). Mean coordinates of the active contact at 12 months follow-up were: Xa=11.6(±1.2); Ya=-2.3(±1.5); Za=-2.6(±1.9). The Euclidian distance from active contact to preoperative target was on average 2.7mm (±1.5) . However, it must be emphasised that neither was the "contact 1" always placed in preoperative target nor did we seek the average positioning error from intended target.

Active contact coordinates differed between subjects (Figure 9). Therefore, active stimulation site was also noted with respect to STN borders: Of the 34 contacts inside STN, 27 were in the dorsal half, seven in ventral half. Ten contacts lay in the medial adjacent structures; seven dorsal and three ventral (study II-paper, figure 2).

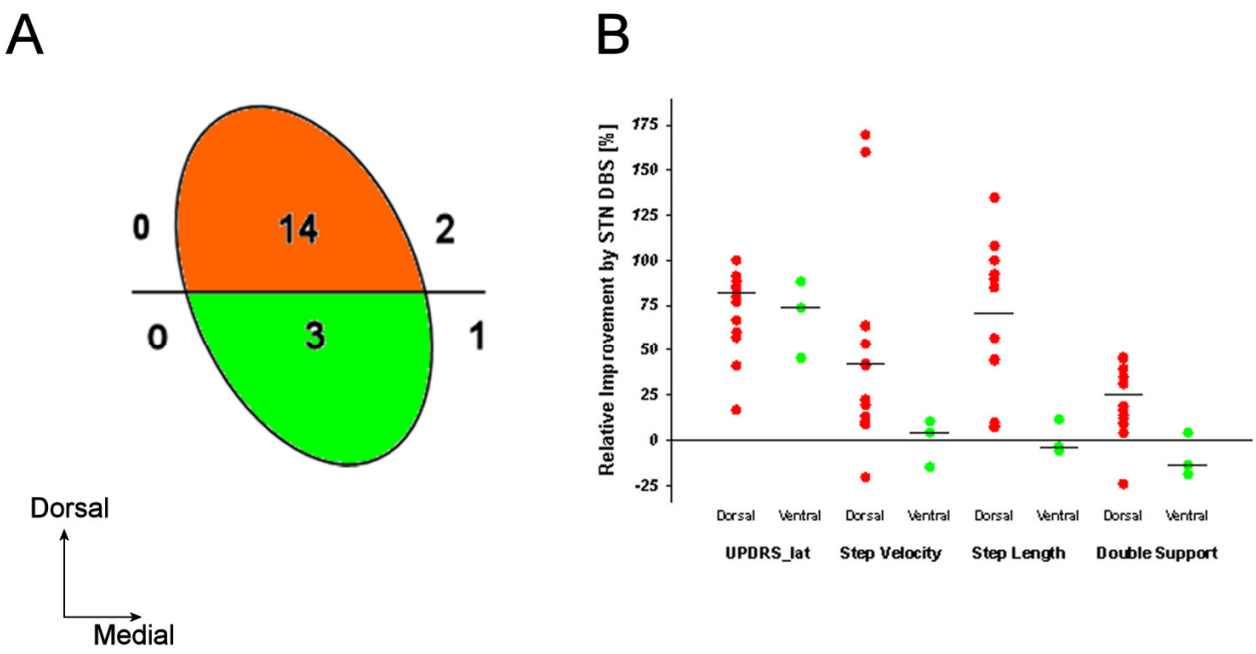



**Figure 10**
A: Position of the active stimulation site in 10 PD patients relative to STN borders. B: Relative change induced by STN DBS on lateralised UPDRS-III score and selected gait parameters with indication of subject change and group-medians. All noted parameters were significantly different ($p<0.05$).

All included patients had improvement of UPDRS-III 12 months post surgery. However, lateralised symptoms score was more improved in dorsal half stimulation compared with ventral half stimulation ($p<0.05$). This statistical significant tendency was also noted in parameters of gait performance that both indicated improvements and deteriorations of gait performance related to stimulation position (Figure 10).

***Comments***

All implantations were guided by micro-electrode recordings (MER) inserted in the targeted path. If recordings did not correspond with STN activity (abrupt increase in background firing (105)) exploring micro-electrode was removed and re-inserted 2mm posterior, anterior, medial or lateral according to preoperative MRI anatomy. Unfortunately, the data were lost and could not be retrieved for post-hoc comparison with MRI-anatomy.

Our survey presents a comparison of gait improvement associated with contact position, but no differences were observed between intra-nucleus versus medial-border stimulation. This could reflect that the volume of activated tissue (VAT) exceeds the resolution for differentiation of stimulated areas in our analysis but also the somatotopic areas influencing gait in the nucleus. VAT has been estimated to be in the range of 5 to 15 $mm^3$ (85). As gait involves several anatomical systems besides lower limb muscles, alleviation of gait symptoms may not be as restricted to precise stimulation-target as single-limb function, e.g. heel tapping, seems to be. Another explanation may be the very small study-sample.

A limitation to our study was also the lack of active contacts lateral to the nucleus. The results do, however, correspond to findings by other groups suggesting the dorsal area of the nucleus is the most clinical effective target for STN DBS.

STUDY III: EFFECT OF STN DBS ON GAIT INITIATION

OFF STN DBS initiation strategy diverged from healthy controls regarding amplitudes of postural adjustments and first and second step lengths (study III-paper, figure 2 + table 2). Both impaired amplitudes OFF DBS as well as the improvements by STN DBS correlated with axial symptom score (Figure 11).

Time-point from initiation signal was given until first movement of weight varied much OFF STN DBS compared with ON DBS and healthy controls. ON DBS the variance was identical to that of healthy controls. Statistically, the group average of first movement time-point did not differ between OFF DBS, ON DBS and healthy controls.

Duration from initiation signal to second heel strike decreased

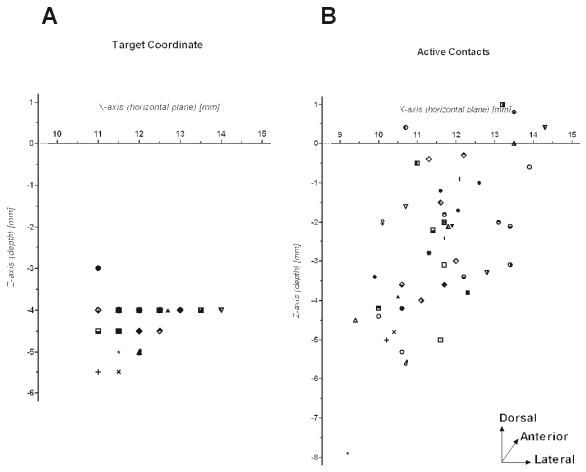



**Figure 9**
Plots of individual target coordinates (A) and localised active stimulation sites (B) relative to mid-commissural point (0;0;0).

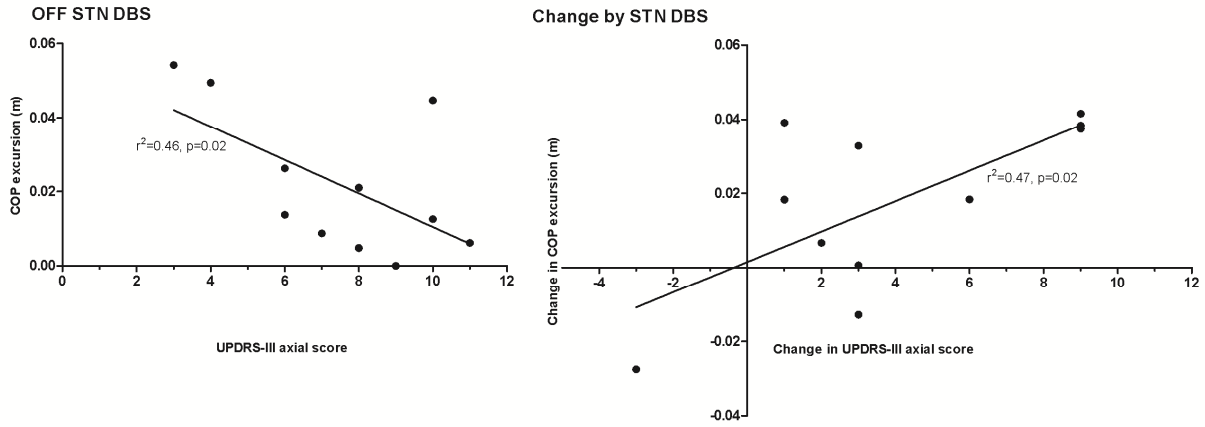



**Figure 11**
Left: Plot of COP excursion vector over UPDRS-III axial score. Right: Plot of change in COP excursion vector over change in UPDRS-III axial score.

with STN DBS although progression-duration of the individual steps were unaffected by PD compared with healthy controls and therefore also unaffected by STN DBS.

HEE-COM distance at the end of first step was not different to that of second step neither OFF nor ON DBS. The improvements by DBS in distance did not reach significance but in both DBS statuses PD patients were impaired relative to healthy controls.

Of the eleven included patients, six were stimulated in the dorsal half and two in the ventral half. Two had the active contact in medial adjacent borders. Localisation was missing in one patient. Statistically, there were no differences in improvements of UPDRS-III axial scores, APA-amplitudes, APA timing, step lengths or step velocities, between STN stimulation areas.

***Comments***

The results of STN DBS effect on gait initiation show an improvement of amplitudes rather than movement durations, consistent with our findings on overground walking. This is also consistent with findings by others, indicating an effect of STN DBS on gait initiation similar to that of levodopa (106).

The study was designed to compare initiation where the person selected first limb, to ensure a self-selected initiation process. Few enrolled patients restrained the possibility of comparing self-selected initiation by the MAS or LAS and thereby rendered search for asymmetry impossible. As mentioned in the introduction, asymmetry in motion has been related to FOG and initiation difficulties.

Studies have shown the selection of leading limb in healthy subjects may be affected by intended goal (107) and near-by obstacles (44) while acute pain alters initiation organisation comparable with PD patients (108). This may indicate a change on cortical level in these subjects.

In our study, five of ten healthy subjects initiated gait with the left leg, though they all declared right-handedness and right-footedness and initiation-signal was placed on the right. Evidence is poor on the subject, but our findings may indicate a random selection among the healthy population, not necessarily correspondent with dominant hand or foot. A pilot survey on healthy elderly gait initiation, performed in our outpatient clinic waiting room, also indicates this phenomenon.

The active stimulation site in relation to initiation process was also evaluated but no differences were found, probably related to the low number of participants.

META-ANALYSIS OF QUANTITATIVE GAIT ANALYSES AND PD DBS

Fifteen studies documented both clinical improvement and specific parameters of gait performance from quantitative gait

**Table 2**

**Characteristics of studies included in the meta-analysis. *) Parentheses indicate time from stimulation change until gait assessment. †) Patients included in gait analyses.**

| Group | Year | Target | n Patients | Months post operative Mean (sd) | Comparison* | Gait analysis system |
|---|---|---|---|---|---|---|
| Nieuwboer et al. | 1998 | Unilat. GPi | 5 | 18 days (6-25) | Pre + post surgery | Foot switches |
| Allert et al. | 2001 | GPi + STN | 10 + 8 | 3 | OFF + ON DBS (½hr) | Ultraflex shoes |
| Defevbre et al. | 2002 | GPi | 10 | 3 | Pre + post surgery | Vicon |
| Faist et al. | 2001 | STN | 8 | 15.4 (10.6) | OFF + ON DBS (1hr) | Treadmill + goniometers |
| Xie et al. | 2001 | STN | 10 | 10.2 (11.2) | OFF + ON DBS (10min) | Foot switches |
| Liu et al. | 2005 | STN | 11 | 16.3 (9.9) | OFF + ON DBS (½hr) | OPTOTRAK |
| Lubik et al. | 2005 | STN | 11 | 22.7 (12.5) | OFF + ON DBS (½hr) | Ultraflex shoes |
| Hausdorff et al. | 2009 | STN | 13 | 12 (7) | OFF + ON DBS (½hr) | Foot switches |
| Johnsen et al. | 2009 | STN | 20(8†) | 17 (6)† | OFF + ON DBS (3hrs) | Vicon |

analyses. The most recent publication from each group was included and three studies therefore excluded (104;109;110). Two studies assessed gait initiation but had no reports on overground walking (106;111). Only three studies presented gait on and off GPi DBS, of which one study presented both GPi and STN DBS (100) and one study only presented unilateral GPi DBS (112). Analyses were therefore restricted to studies documenting STN DBS effect. Also, data from our own studies were added to the analyses. Table 2 present characteristics of included studies. Referenced figures in the following are presented in the appendix B.

***Effect on UPDRS-III***

Seven studies presented exact figures of the UPDRS-III both off and on STN DBS, off medication, enabling comparison. Other studies only documented relative improvements in percent (100;103)(figure B.1). Five studies included data of UPDRS-III item 29: "Gait" (figure B.2).

UPDRS-III is significantly improved by STN DBS ($p<0.001$)(figure B.1). One study did not present improvement of UPDRS-III item 29 (113) but meta-analysis show that "Gait" is significantly improved by STN DBS (figure B.2).

***Effect on Gait Parameters***

All included studies presented the effect on gait velocity and cadence. Six of the STN DBS studies presented stride length, other studies documented step lengths. Four studies presented step time, stride time by three. Step time was chosen as duration-parameter. Double support phase was inconsistently presented in percent of gait cycle or absolute seconds and could therefore not be evaluated.

Stratified analyses indicates only STN DBS improves gait velocity ($p<0.001$)(figure B.3). GPi DBS has little or no effect on gait velocity ($p=0.21$) or cadence ($p=0.53$), while STN DBS may increase steps per minute ($p=0.03$). Interestingly, only one study document significant increase in cadence by DBS (figure B.4).

Stride length is significantly improved by STN DBS ($p<0.01$) but not by GPi DBS (112;114)(figure B.5). Step time was unaffected by DBS in all included studies ($p=0.22$)(figure B.6) and by PD (100;115).

***Comments***

Documentation of STN DBS effect on gait performance and balance during gait was sparse before year 2005, where we initiated our investigations. Indeed, to make a fair estimate of DBS effect on gait performance, the meta-analysis was performed on studies with different approaches to gait analyses with differences in analysis system and comparison of pre- with postoperative vs. OFF with ON DBS.

Differences in methodology may increase the heterogeneity of study outcomes and thereby also comparability. Also, the exact inference of STN DBS on kinematic and kinetic parameters in order to maintain balance during steady-state gait as well as the transition from up-right stance to gait initiation is very sparsely documented.

REVIEW OF MOST OPTIMAL STIMULATION SITE

Review of relevant literature revealed 13 studies of interest (Table 3).

Most studies presented evaluation of clinical outcome related to secondary localisation of the active contact. Only one study presented evaluation of different target areas (116). Apart from our own study, one other study presented the clinical outcome in different stimulation areas (117). Localisation-method differed between studies; however overall comparability was assumed fair. All studies used the UPDRS-III for evaluation of outcome (118). Four studies did not present exact figures of clinical outcome and was therefore omitted from plots (119-122).

**Table 3**

**Review of stimulation site and localisation method. UPDRS-II improvement is presented as published or calculated on basis of published data. Coordinates are presented as published as mean ± standard deviation except Starr et al. who presented mean ± standard error. All coordinates are relative to mid-commissural point (mid-ACPC). MER: Micro electrode recording, MRI: Magnetic resonance imaging, STN: Subthalamic nucleus, UPDRS-III: Unified Parkinson's disease Rating Scale motor score, ZI: Zona incerta.**

| Group | Year | n active contacts | UPDRS-III improvement | Target | X Mean (sd) | Y Mean (sd) | Z Mean (sd) | Localisation method |
|---|---|---|---|---|---|---|---|---|
| Lanotte et al. | 2002 | 28 | n/a | STN | 12.3 (0.9) | -1.7 (0.9) | -1.7 (1.5) | From target and MER |
| Saint-Cyr et al. | 2002 | 54 | n/a | STN | 11.5 (1.7) | -2.1 (1.5) | -1.2 (1.8) | -\|\|- |
| Starr et al. | 2002 | 20 | 19% | STN | 11.8 (0.2) | -3.8 (0.2) | -3.8 (0.2) | -\|\|- |
| Hamel et al. | 2003 | 49 | n/a | STN | 12.8 (1.0) | -1.6 (2.1) | -1.6 (2.1) | -\|\|- |
| Littlechild et al. | 2003 | 50 | 48% | STN | 13.3 | -0.6 | -1.2 | -\|\|- |
| Herzog et al. | 2004 | 5 | 49% | Above STN | 13.6 (1.1) | -1.9 (1.5) | -0.4 (0.9) | -\|\|- |
| - \|\| - | | 15 | 65% | Dorsal STN | 12.7 (0.7) | -2.3 (1.1) | -2.1 (1.4) | -\|\|- |
| - \|\| - | | 5 | 63% | STN | 12.9 (1.5) | -2.1 (1.3) | -1.9 (1.2) | -\|\|- |
| Zonenshayn et al. | 2004 | 62 | 64% | STN | 13.3 (2.3) | -0.5 (2.1) | -0.1 (2.8) | -\|\|- |
| Andrade-Souza et al. | 2005 | 28 | 52% | STN | 12.1 (1.5) | -2.4 (1.6) | -2.4 (1.5) | -\|\|- |
| Hamid et al. | 2005 | 54 | n/a | STN | 11.7 (1.3) | -2.1 (1.4) | -3.8 (1.2) | Localised on MRI |
| Breit et al. | 2006 | 60 | 66% | STN | 11.9 (1.2) | -1.6 (1.5) | -2.6 (1.2) | -\|\|- |
| Godinho et al. | 2006 | 56 | 63% | STN | 11.4 (1.1) | -1.9 (0.9) | -2.3 (1.1) | From target and MER |
| Plaha et al. | 2006 | 17 | 55% | STN | 12.4 (1.2) | -2.1 (1.3) | -2.3 (0.8) | Intraoperative MRI |
| - \|\| - | | 20 | 61% | Medial to STN | 11.4 (1.1) | -3.0 (0.8) | -2.1 (0.9) | -\|\|- |
| - \|\| - | | 27 | 72% | Caudal ZI | 14.0 (1.6) | -5.8 (1.5) | -2.1 (1.1) | -\|\|- |
| Pollo et al. | 2007 | 62 | 39% | STN | 12.0 (1.6) | -2.3 (1.6) | -2.6 (1.7) | From target and MRI |
| Johnsen et al. | 2010 | 44 | 62% | STN | 11.6 (1.3) | -2.4 (1.2) | -1.9 (1.6) | Localised on MRI |

Plot of the average active contact distribution of all studies revealed large diversity in location relative to the mid-commissural point, i.e. STN stimulation in one study was located close to medial stimulation in another study (Figure 12). Most relative improvement was seen in stimulation of caudal ZI (116). The study documenting most ventral stimulation, presented least improvement post-surgery (123). None of the studies with extreme coordinate positions presented higher incidences of side-effects to stimulation, probably reflecting consensus in target planning and clinical evaluation of stimulation during operation.

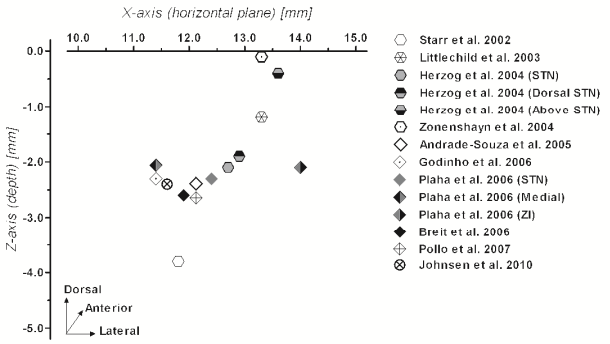



**Figure 12**
Plot of published active stimulation sites for STN DBS relative to mid-commissural point (mid-AC/PC) (0;0;0) of studies presenting UPDRS-III improvement (Starr et al. 2002;Littlechild et al. 2003;Herzog et al. 2004;Zonenshayn et al. 2004;Andrade-Souza et al. 2005;Breit et al. 2006;Godinho et al. 2006;Plaha et al. 2006;Pollo et al. 2007;Johnsen et al. 2010).

***Comments***

The systematic review indicates the need of a different approach for documenting the active stimulation site in relation to outcome. Most studies presented the overall effect on total UPDRS-III score, thereby comparing the effect of DBS position in either hemisphere with general motor-performance. Apart from our own study, two studies (116;117) used the lateralised symptom-score to compare individual hemisphere-improvement and proved differential effect dependent on stimulation site. Divergent results increase the need for further exploration and, the relationship between stimulation point and distinct motor improvement of gait has not previously been reported. Therefore, we aimed to evaluate the possible relationship of clinical outcome and gait improvement with stimulation site relative to the STN borders (paper-II).

**DISCUSSION WITH FUTURE PERSPECTIVES**

THE EFFECT ON GAIT PERFORMANCE

We aimed to quantify the effect of STN DBS on PD gait and gait initiation with quantitative gait analyses without medication, "OFF" and "ON" DBS.

Consistent with other studies, we found that bilateral STN DBS increases step length and gait velocity during overground walking. Cadence and step time was not affected. Improvement in kinematics and kinetics were in correspondence with previous quantitative PD gait analyses and in our study of gait initiation, amplitudes of movements rather than durations of movements were improved by STN DBS.

A novel documentation from our study is the relation of gait asymmetry to postural instability during gait. To place the foot ahead of COM, the limb must be ejected from the ground and then swung forward. At the same time, the upper body also moves forward in order to progress motion of COM (35;36). In our study of overground walking, some patients even placed the most affected limb behind COM, and so the body centre was ahead of the support area and balance impaired (131). This may imply that instability and festination was a result of improper push-off and excessive trunk-inclination. We did not find this asymmetry in gait initiation. However, the HEE-COM distance was decreased compared with healthy controls and improved ON STN DBS. The HEE-COM distance may therefore be a measure of festinative and propulsive gait dependent on both trunk inclination and hypokinetic movements.

We suggest STN DBS improves hypokinesia in gait, thus improving propulsion.

Amongst others, the meta-analysis revealed that STN DBS improves gait, assessed by the UPDRS-III item 29. Also, a consistent finding was the improvement of step lengths rather than durations which indeed was not changed by STN DBS in any of the studies.

It has been a matter of debate whether STN DBS impacts cadence. Our meta-analysis shows a slight increase in cadence by STN DBS. This has been claimed an "improvement" (132;133) although it may be discussed what constitutes an improvement or deterioration of cadence: increase or decrease of steps per minute? In festination, cadence is high but amplitude low (134) and improvement would be a change toward the opposite.

The main deficit of PD gait is the lack of linearity in stride-length/cadence relationship; stride-length is impaired but the change in cadence withheld (60). Therefore, the increase in cadence might rather reflect an attempt of faster walking.

Step-length may be regarded measure of hypokinesia and an important contributor to poor balance during gait. In both our studies of gait performance, we found increased amplitude of step-length by STN DBS. It would therefore be suspected that DBS improves the length/cadence-relationship. To assess this, future studies should include comparison of PD gait during different self-paced gait velocities; i.e. slow, faster and fastest possible.

The decrease of amplitude asymmetry could be explained by either difference in stimulation settings between the two hemispheres or in optimal electrode positioning. However, stimulation settings were comparable between hemispheres and HEE-COM improvement did not differ between stimulation sites. We were not able to assess gait-asymmetry during gait initiation.

Asymmetry and bilateral coordination in PD gait has been related to FOG and fear of falling (64;65). Step coordination becomes asymmetric with age and is further deteriorated in PD patients with FOG but not in non-freezers and is not associated to spatio-temporal asymmetry (135;136).

In our investigation of overground walking in non-freezers dynamic asymmetry (joint angles and moments) was associated with spatial parameters (HEE-COM distance and step lengths) but not with temporal parameters. This may suggest a difference in anatomical origin of the deficits.

Bilateral coordination and activation of successive movements originate from local movement centres at cerebellar and spinal level (137), while the amplitude of movements may originate from higher levels of the central nervous system (33). Deteriorated coordination and activation suggests a temporal affection rather than a spatial defect. Our results from studies in non-freezers therefore indicate an improvement of facilitated movements on higher level while FOG may originate outside the basal ganglia.

It can be speculated what defines FOG; the festinative gait with high cadence and small amplitudes or the increased time to perform a desired motion i.e. an akinetic phase before motion

onset (138;139). This latter gait disability is however also seen in gait of depressed patients, not complaining of FOG (140). We did not control for depression in neither of our analyses and therefore cannot rule out a possible inference of psychomotor slowness on reaction times and movement durations. However, as these were comparable to healthy elderly controls, the inference may be regarded minimal.

To elucidate this topic further, future analyses could involve comparison of overground gait and standing gait initiation in PD freezers vs. non-freezers as well as PD vs. depressed patients, with special emphasis on differences in movement onset, amplitudes and durations.

DEEP BRAIN STIMULATION SITE

We suggest the active stimulation site impacts the effect of stimulation on PD gait. However, a limitation to our study was the lack of stimulation sites in the lateral adjacent structures such as caudal ZI or H2 in Forel's field. This has been suggested to improve PD symptoms better than STN stimulation (116). Any randomized trial on different stimulation sites may, however, seem unethical given the known side-effects to stimulation in the CI such as muscle contractions or slurred speech but also given the known deficits in actually hitting the intended target within more than half a millimetre in best scenarios (141). Therefore, future analyses on the most optimal stimulation site may continue as postoperative surveys. However, investigations for optimisation of the peri-operative scan-parameters as well as increasing knowledge on the actual position of the electrode in the artefact should continue.

Knowledge on the actual stimulation site may act to increase our knowledge of the functionality of stimulated areas. Future studies should assess correlation of stimulation site with neuropsychiatric changes and adverse events after stimulation and frontal executive functions (142). Furthermore, first when a common area for stimulation in a group of patients can be assumed, randomized controlled trials for optimization of stimulation settings can performed. Thereby, e.g. low-frequency DBS can be compared with high-frequency DBS for improvement of FOG.

THE EFFECT ON MOTOR PLANNING

Functional neuroimaging of PD patients and healthy subjects suggest an impaired recruitment of both cortical and subcortical motor regions regulating kinematic parameters of movements in PD (55;56). Prior to any movement of the limbs or body weight, the bereitschaft potential (BP) is registered, originating from the SMA. The BP may reflect cortical activation correspondent with APA-initiation (54).

It was recently suggested that disruption of SMA in healthy subjects by 1Hz repetitive transcranial magnetic stimulation (rTMS) would lead to impairment of APA timing and amplitude, comparable to the PD state (54). Interestingly, in both healthy and PD subjects APA duration was shortened but APA amplitude was unaffected by rTMS. Thus gait was initiated quicker when the SMA-BG projection was disconnected. This could suggest that the cortex prioritizes sensory feedback systems and pre-programming induced by the dorsal and mesial pre-frontal cortices (56).

The effect of rTMS on APA is contrary to our and previous findings by STN DBS, that rather suggest an improvement of APA amplitudes but no affection of APA-timing (106;111). It might seem that turning "off" the basal ganglia by rTMS shortens movement duration time. Turning them "on" with STN DBS increases movement amplitudes and improves hypokinesia.

It is suggested that DBS restores pathological signalling in the ß and γ frequency bands (Brown 2006). These bands may act to control motor performance through inhibition of movement (ß-activity) or activation of movements (γ-activity), relating ß-activity to both rigidity and bradykinesia in PD (25;143). However, if indeed high frequency STN DBS changes the neuronal signalling in the BG and connected systems, it would be suspected that also muscle tone is changed – as observed in decreased rigidity (25) – and this may increase amplitude in standing initiation and overground gait.

Progress in development of non-invasive cortical and subcortical measurement methods such as magneto-encephalography may increase our understanding of LFP origin and relevance for movement generation in both healthy and diseased basal ganglia. It would be of great interest to compare the possible change in LFPs by STN DBS in the basal ganglia and to search for the possible influence of active stimulation site.

The descending pathways from the GPi, the SNr and also the STN have only been touched briefly in this thesis. The BG descend signals to the PPN and mesencephalic locomotor region (MLR) which in turn, under inhibitory influence of the GPi/SNr, activates or deactivates the relevant motor pathways and finally reach the spinal cord via reticulo-spinal tracts (144). On spinal level, these descending pathways act to increase or decrease muscle-tone, probably related to burst-firing activities of the non-cholinergic (glutamatergic) PPN-neurones (53). It has been shown that low frequency burst-stimulation of the human sacral and cervical cords in level of lower and upper limb motor-centres resembling the burst activity of PPN slowly builds up muscle tone and eventually initiate gait-related movements (47). Furthermore, studies of decerebrated cats have shown the build-up of a stepping-pattern after seconds of electrical stimulation with gradually increased current in the PPN. On the other hand, if the current was applied suddenly, the result was a startle-response followed by stepping or wild running (145). Low frequency stimulation (LFS) in the PPN and tegmental areas has been suggested to improve PD symptoms and gait in patients with severe gait disabilities and especially FOG has been emphasized as indication (146;147). However, until now only sleep improvement has been quantitatively documented (148). The exact impact of low frequency PPN stimulation on specific parameters of gait performance, e.g. step length or APA amplitudes and durations, remains unresolved.

| ID no. | Enrolled in study no.* | Gender | PD Onset | | Implantation | | Medication† | | Stimulation Settings ‡ | | | | UPDRS-IIIΔ | | Exclusion Criteria, Study I + III |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Pre | Post | Amp. [V] | | Freq. | PW | Pre | Post | |
| | | | Year | Side | Age | Date | LDEQ | LDEQ | Ch 1 | Ch 2 | [Hz] | [µsec.] | | | |
| 01 | II* | Male | 1995 | Right | 42 | Nov. 02 | 1,220 | 1,050 | - | - | - | - | 39 | 11 | Did not respond |
| 02 | II* | Female | 1981 | Right | 62 | Jan. 03 | 575 | 675 | - | - | - | - | 65 | 31 | Other Gait affection |
| 03 | I* +II +III* | Female | 1993 | Right | 64 | Feb. 03 | 538 | 275 | 3.2 | 2.6 | 160 | 60 | 32 | 9 | |
| 04 | I +II + III | Male | 1984 | Left | 60 | Mar. 03 | 1,871 | 1,029 | 3.2 | 3.2 | 165 | 60 | 45 | 22 | |
| 05 | II | Male | 1981 | Right | 60 | Apr. 03 | 1,829 | 1,429 | 3.3 | 3.1 | 155 | 60 | 68 | 20 | Dead |
| 06 | II | Male | 1991 | Left | 52 | Sep. 03 | 1,050 | 980 | 3.3 | 3.3 | 160 | 60 | 40 | 17 | Dementia |
| 07 | I* +II+III* | Female | 1993 | Left | 62 | Sep. 03 | 1,105 | 508 | 2.6 | 3.0 | 150 | 60 | 42 | 11 | |
| 08 | I +II + III | Male | 1994 | Left | 59 | Sep. 03 | 1,750 | 1,150 | 2.2 | 3.5 | 160 | 60 | 48 | 17 | |
| 09 | I* +II+III* | Female | 1988 | Right | 48 | Oct. 03 | 921 | 790 | 3.5 | 3.5 | 160 | 60 | 67 | 39 | |
| 10 | II | Male | 1987 | N/A | 66 | Oct. 03 | 1,240 | 1,125 | 3.5 | 3.3 | 160 | 60 | 42 | 36 | Dementia |
| 11 | I +II +III* | Female | 1990 | Right | 65 | Nov. 03 | 1,296 | 355 | 2.9 | 2.9 | 145 | 60 | 31 | 15 | |
| 12 | I* +II+III* | Male | 1991 | Right | 67 | Dec. 03 | 1,350 | 340 | 3.1 | 2.3 | 135 | 60 | 53 | 22 | |
| 13 | I +II + III | Male | 1995 | Left | 57 | Mar. 04 | 815 | 930 | 2.8 | 3.7 | 140 | 60 | 33 | 8 | |
| 14 | II | Female | 1988 | Right | 64 | Mar. 04 | 460 | 460 | 3.3 | 3.3 | 145 | 60 | 39 | 18 | Dead |
| 15 | I +II* +III | Male | 1996 | Left | 40 | Apr. 04 | 1,125 | 980 | 3.3 | 3.3 | 170 | 60 | 43 | 12 | |
| 16 | I +II + III | Male | 1994 | Right | 59 | May 04 | 500 | 200 | 3.8 | 3.6 | 175 | 60 | 45 | 20 | |
| 17 | I* +II+III* | Female | 1993 | Right | 68 | Aug. 04 | 1,515 | 1,607 | 3.3 | 3.3 | 145 | 60 | 43 | 15 | |
| 18 | I +II + III | Female | 1992 | Right | 61 | Sep. 04 | 1,660 | 950 | 3.5 | 3.2 | 150 | 60 | 60 | 14 | |
| 19 | I +II + III | Female | 1982 | Left | 56 | Sep. 04 | 905 | 780 | 3.7 | 3.7 | 155 | 60 | 41 | 9 | |

| Enrolled in study no.* | Gender | PD Onset | | Implantation | | Medication† | | Stimulation Settings ‡ | | | | UPDRS-IIIΔ | | Exclusion Criteria, Study I + III |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Year | Side | Age | Date | Pre LDEQ | Post LDEQ | Amp. [V] Ch 1 | Amp. [V] Ch 2 | Freq. [Hz] | PW [µsec.] | Pre | Post | |
| I*+II+III* | Male | 1996 | Right | 60 | Sep. 04 | 850 | 786 | 3.5 | 3.5 | 140 | 60 | 30 | 3 | |
| II | Male | 1992 | Right | 68 | Nov. 04 | 1,239 | 510 | 3.3 | 3.5 | 150 | 60 | 49 | 23 | Other Gait affection |
| II* +III | Female | 1994 | Right | 68 | Dec. 04 | 380 | 210 | 3.5 | 3.4 | 140 | 60 | N/A | N/A | |
| II + III* | Female | 1995 | Left | 67 | Feb. 05 | 1,353 | 880 | 3.4 | 3.4 | 155 | 60 | 62 | 25 | |
| II + III | Male | 1990 | Left | 65 | Feb. 05 | 1,110 | 940 | 3.5 | 3.0 | 150 | 60 | 40 | 8 | |
| - | Female | 1991 | N/A | 51 | Oct. 05 | 750 | 0 | - | - | - | - | - | - | Refused Gait Analysis |
| - | Male | 1993 | Left | 55 | Oct. 05 | 1,321 | 480 | - | - | - | - | - | - | Refused Gait Analysis |
| - | Male | 1994 | Right | 69 | May 06 | 918 | 450 | - | - | - | - | - | - | Refused Gait Analysis |
| - | Male | 1992 | Left | 64 | May 06 | 1,380 | 1,355 | - | - | - | - | - | - | Other Gait affection |
| - | Female | 1990 | Right | 63 | Jun. 06 | 1,250 | 1,000 | - | - | - | - | - | - | Other Gait affection |
| II + III | Male | 1992 | Left | 67 | Nov. 06 | 1,050 | 500 | 2.5 | 3.6 | 150 | 60 | 25 | 8 | |
| II + III | Male | 1981 | Right | 59 | Apr. 07 | 1,210 | 500 | 3.1 | 3.3 | 130 | 60 | 47 | 25 | |
| II* + III* | Male | 1993 | Right | 54 | Jun. 07 | 1,700 | 750 | - | - | - | - | 39 | 13 | |
| - | Female | 1992 | Left | 67 | Sep. 07 | 1,968 | N/A | - | - | - | - | - | - | Other Gait affection |
| - | Male | 1997 | Right | 53 | Sep. 07 | 4,114 | N/A | - | - | - | - | - | - | Refused Gait Analysis |

**Table 1: Patient characteristics**

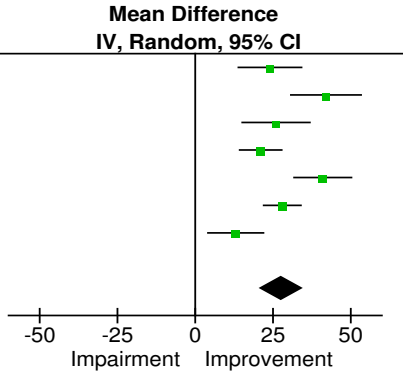
***) Patient was excluded from analyses: #01,#02 ,#32: Surgery performed with other protocol, #03,# 11,#32: Computer error, #07,#09,#12,#23: Patient unable to walk OFF STN DBS, #15: No peri-operative MRI available, #17: Patient only able to walk with shoes, #20: Patient not "off" without stimulation (UPDRS-III change <25%), #22: 12 months UPDRS-III unavailable. †) Total daily intake of levodopa and dopamine agonists combined. 100mg levodopa = 140mg levodopa cr. = 1mg pergolide = 1 mg pramipexole = 2mg cabergoline. ‡) There were no statistical differences in stimulation amplitude between hemispheres. Stimulation frequency and pulse-widths (PW) were identical on both hemispheres. Δ) Data presented in medication "off" state pre-surgery and at 12 months postoperative**

**APPENDIX B**

B-1: EFFECT ON UPDRS – III

| Study or Subgroup | OFF DBS Mean | SD | Total | ON DBS Mean | SD | Total | Weight | Year |
|---|---|---|---|---|---|---|---|---|
| Xie et al. STN | 43 | 13 | 10 | 19 | 10 | 10 | 13.5% | 2001 |
| Faist et al. STN | 49 | 16 | 8 | 7 | 3 | 8 | 12.7% | 2001 |
| Krystkowiak et al. STN | 52 | 16 | 10 | 26 | 7 | 10 | 13.0% | 2003 |
| Liu et al. STN | 42 | 7 | 11 | 21 | 9 | 11 | 15.9% | 2005 |
| Ferrarin et al. STN | 62 | 11 | 10 | 21 | 10 | 10 | 14.2% | 2005 |
| Johnsen et al. STN | 44 | 11 | 20 | 16 | 8 | 20 | 16.4% | 2009 |
| Hausdorff et al. STN | 31 | 13 | 13 | 18 | 10 | 13 | 14.4% | 2009 |
| **Total (95% CI)** | | | **82** | | | **82** | **100.0%** | |

Heterogeneity: Tau² = 71.18; Chi² = 28.61, df = 6 (P < 0.0001); I² = 79%
Test for overall effect: Z = 7.58 (P < 0.00001)

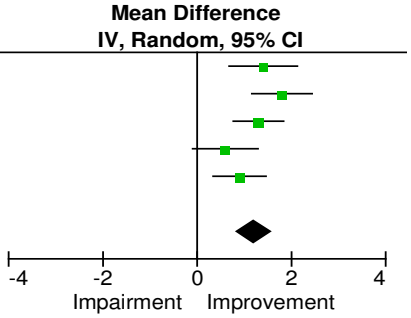



Total UPDRS-III is in general decreased with 25.75 points by DBS [95%CI: 22.79;28.72]. NB! Johnsen et al. data include all patients assessed during the PhD studies.

B-2: EFFECT ON UPDRS-III ITEM 29 "GAIT"

| Study or Subgroup | OFF DBS Mean | SD | Total | ON DBS Mean | SD | Total | Weight | Year |
|---|---|---|---|---|---|---|---|---|
| Krystkowiak et al. STN | 2.2 | 0.6 | 10 | 0.8 | 1 | 10 | 17.0% | 2003 |
| Lubik et al. STN | 2.4 | 0.9 | 10 | 0.6 | 0.5 | 10 | 19.6% | 2005 |
| Ferrarin et al. STN | 2.5 | 0.5 | 12 | 1.2 | 0.8 | 12 | 23.2% | 2005 |
| Hausdorff et al. STN | 1.4 | 0.9 | 13 | 0.8 | 0.9 | 13 | 17.9% | 2009 |
| Johnsen et al. STN | 2.3 | 0.9 | 20 | 1.4 | 0.9 | 20 | 22.3% | 2009 |
| **Total (95% CI)** | | | **65** | | | **65** | **100.0%** | |

Heterogeneity: Tau² = 0.10; Chi² = 7.83, df = 4 (P = 0.10); I² = 49%
Test for overall effect: Z = 6.04 (P < 0.00001)

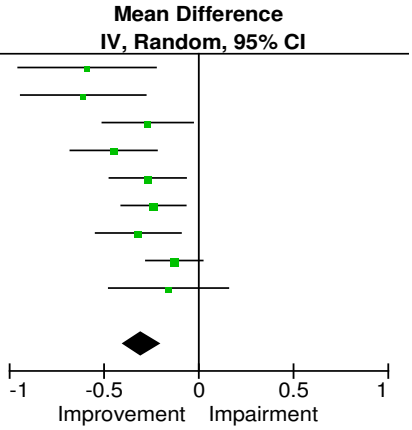



All studies but one show DBS improve UPDRS-III item 29 "gait". NB! Johnsen et al. data include all patients assessed during PhD studies.

B-3: EFFECT ON GAIT VELOCITY

| Study or Subgroup | OFF DBS Mean | SD | Total | ON DBS Mean | SD | Total | Weight | Year |
|---|---|---|---|---|---|---|---|---|
| Xie et al. STN | 0.49 | 0.4 | 8 | 1.08 | 0.34 | 8 | 5.9% | 2001 |
| Allert et al. STN | 0.35 | 0.24 | 8 | 0.96 | 0.41 | 8 | 6.9% | 2001 |
| Faist et al. STN | 0.66 | 0.31 | 10 | 0.93 | 0.23 | 10 | 10.7% | 2001 |
| Krystkowiak et al. STN | 0.5 | 0.26 | 10 | 0.95 | 0.26 | 10 | 11.4% | 2003 |
| Liu et al. STN | 0.68 | 0.26 | 11 | 0.95 | 0.22 | 11 | 13.1% | 2005 |
| Lubik et al. STN | 0.43 | 0.24 | 12 | 0.67 | 0.18 | 12 | 15.6% | 2005 |
| Ferrarin et al. STN | 0.56 | 0.24 | 10 | 0.88 | 0.27 | 10 | 11.7% | 2005 |
| Johnsen et al. STN | 0.98 | 0.18 | 8 | 1.11 | 0.12 | 8 | 17.3% | 2009 |
| Hausdorff et al. STN | 0.6 | 0.42 | 13 | 0.76 | 0.4 | 13 | 7.4% | 2009 |
| **Total (95% CI)** | | | **90** | | | **90** | **100.0%** | |

Heterogeneity: Tau² = 0.01; Chi² = 13.54, df = 8 (P = 0.09); I² = 41%
Test for overall effect: Z = 5.95 (P < 0.00001)

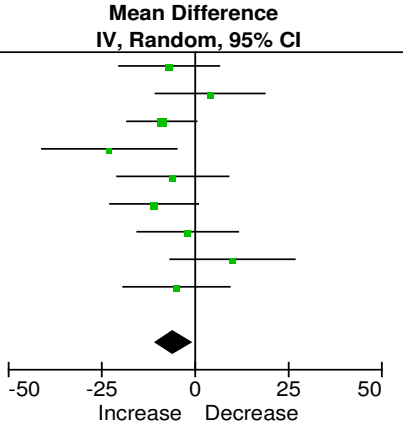



STN DBS improves gait velocity (m/Sec).

B-4: EFFECT ON CADENCE

| Study or Subgroup | OFF DBS Mean | SD | Total | ON DBS Mean | SD | Total | Weight | Year |
|---|---|---|---|---|---|---|---|---|
| Xie et al. STN | 99 | 18 | 10 | 106 | 12 | 10 | 11.3% | 2001 |
| Faist et al. STN | 122 | 18 | 8 | 118 | 11 | 8 | 9.9% | 2001 |
| Allert et al. STN | 110 | 12 | 8 | 119 | 6 | 8 | 19.1% | 2001 |
| Krystkowiak et al. STN | 93 | 25 | 10 | 116 | 15 | 10 | 6.9% | 2003 |
| Lubik et al. STN | 95 | 18 | 10 | 101 | 16 | 10 | 9.5% | 2005 |
| Liu et al. STN | 91 | 17 | 12 | 102 | 12 | 12 | 13.8% | 2005 |
| Ferrarin et al. STN | 105 | 14 | 11 | 107 | 18 | 11 | 11.2% | 2005 |
| Johnsen et al. STN | 128 | 18 | 8 | 118 | 16 | 8 | 7.9% | 2009 |
| Hausdorff et al. STN | 100 | 20 | 13 | 105 | 17 | 13 | 10.3% | 2009 |
| **Total (95% CI)** | | | **90** | | | **90** | **100.0%** | |

Heterogeneity: Tau² = 13.03; Chi² = 10.20, df = 8 (P = 0.25); I² = 22%
Test for overall effect: Z = 2.21 (P = 0.03)

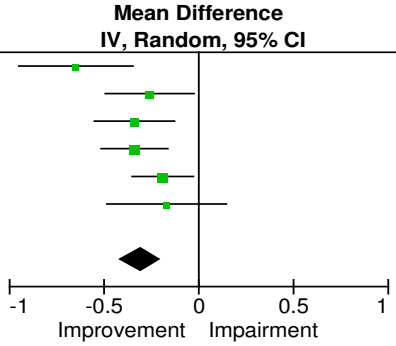



STN DBS improves cadence (steps/min).

B-5: EFFECT ON STRIDE LENGTH

| Study or Subgroup | OFF DBS Mean | SD | Total | ON DBS Mean | SD | Total | Weight | Year |
|---|---|---|---|---|---|---|---|---|
| Faist et al. STN | 0.34 | 0.21 | 8 | 0.99 | 0.38 | 8 | 10.9% | 2001 |
| Xie et al. STN | 0.8 | 0.32 | 10 | 1.06 | 0.2 | 10 | 15.6% | 2001 |
| Krystkowiak et al. STN | 0.63 | 0.23 | 10 | 0.97 | 0.25 | 10 | 17.8% | 2003 |
| Ferrarin et al. STN | 0.68 | 0.2 | 10 | 1.02 | 0.2 | 10 | 21.8% | 2005 |
| Johnsen et al. STN | 0.94 | 0.21 | 8 | 1.13 | 0.1 | 8 | 23.7% | 2009 |
| Hausdorff et al. STN | 0.69 | 0.41 | 13 | 0.86 | 0.41 | 13 | 10.2% | 2009 |
| **Total (95% CI)** | | | **59** | | | **59** | **100.0%** | |

Heterogeneity: Tau² = 0.01; Chi² = 8.09, df = 5 (P = 0.15); I² = 38%
Test for overall effect: Z = 5.29 (P < 0.00001)

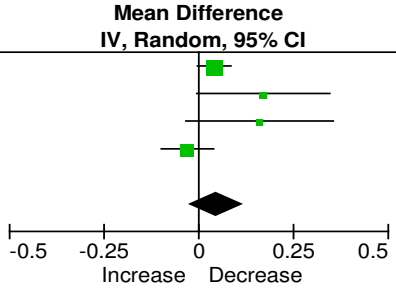



STN DBS improves stride length (m).

B-6: EFFECT ON STEP TIME

| Study or Subgroup | OFF DBS Mean | SD | Total | ON DBS Mean | SD | Total | Weight | Year |
|---|---|---|---|---|---|---|---|---|
| Allert et al. STN | 0.55 | 0.06 | 8 | 0.51 | 0.02 | 8 | 41.7% | 2001 |
| Krystkowiak et al. STN | 0.7 | 0.24 | 10 | 0.53 | 0.15 | 10 | 12.9% | 2003 |
| Lubik et al. STN | 0.77 | 0.34 | 12 | 0.61 | 0.05 | 12 | 11.1% | 2005 |
| Johnsen et al. STN | 0.47 | 0.07 | 8 | 0.5 | 0.07 | 8 | 34.3% | 2009 |
| **Total (95% CI)** | | | **38** | | | **38** | **100.0%** | |

Heterogeneity: Tau² = 0.00; Chi² = 7.30, df = 3 (P = 0.06); I² = 59%
Test for overall effect: Z = 1.23 (P = 0.22)




Step time (sec.) is reported to increase and decrease with DBS. Meta-analysis shows no effect by STN DBS on the parameter.

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