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# The effect of deep brain stimulation randomized by site on balance in Parkinson's disease

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## Abstract

**Background—**The effect of the surgical site of Deep Brain Stimulation (DBS) on balance and gait in Parkinson's Disease (PD) is uncertain. This is the first double-blind study of subjects randomized to either the Subthalamic Nucleus (STN, N=14) or Globus Pallidus interna (GPi, N=14) who were assessed on a range of clinical balance measures.

**Methods—**Balance testing occurred before and 6 months post-surgery. A control PD group was tested over the same time period without surgery (N=9). All subjects were tested on and off medication and DBS subjects were also tested on and off DBS. The Postural Instability and Gait Disability items of the Unified Parkinson's Disease Rating Scale and additional functional tests we call the Balance and Gait scale were assessed. Activities of Balance Confidence and Activities of Daily Living questionnaires were also recorded.

**Results—**Balance was not different between the best-treated states before and after DBS surgery for both sites. Switching DBS on improved balance scores and scores further improved with medication compared to the off state. The GPi group showed improved performance in the post-surgery off state and better ratings of balance confidence after surgery compared to the STN group.

**Conclusions—**Clinical measures of balance function for both the STN and GPi sites showed that balance did not improve beyond the best medically-treated state prior to surgery. Both clinical balance testing in the OFF/OFF state and self-reported balance confidence after surgery showed better performance in the GPi than the STN group.

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**AUTHOR ROLES**

Dr St George was involved in data collection, statistical analysis design and execution and writing the first draft of the manuscript. Dr Carlson-Kuhta was involved with conception, organization, recruitment, data collection, and review and critique of the manuscript. Professor Nutt was involved in planning, interpretation of results and editing the manuscript. Doctor Hogarth was involved with planning, recruitment and editing the manuscript. Professor Burchiel performed the surgeries and was involved with editing the manuscript. Professor Horak oversaw all aspects of the study from conception, organization, data collection, planning and final manuscript preparation.

**FINANCIAL DISCLOSURES**

None of the authors have any conflicts of interest that relate to the research covered in this article.

**Keywords**

Parkinson's disease; DBS; postural control; clinical assessment

## INTRODUCTION

The stimulation site of Deep Brain Stimulation (DBS) in Parkinson's Disease (PD) is commonly the Subthalamic Nucleus (STN) and less commonly the Globus Pallidus interna (GPi). Meta-analysis shows some improvement in the postural instability and gait disability (PIGD) items of the Unified Parkinson's Disease Rating Scale (UPDRS III)[1] for both sites within the first year after surgery[2]. However, it is difficult to make firm conclusions about how the DBS site affects balance as there are far fewer GPi studies. This randomised controlled study measures the effect of DBS on balance off and on medication, and off and on DBS, before and after surgery, to determine how these therapies interact in both sites.

The PIGD score only assesses some of the balance and gait deficits experienced in PD. It does not assess the reduced forward and backward limits of stability during standing[3], impaired motor sequencing during postural transitions[4,5] freezing particularly when initiating gait, turning, and passing through doorways[6,7], reduced arm swing when walking[8,9], or the extent that voluntary attention compensates for a loss of postural tone which can be gauged with a secondary cognitive task[10]. We have combined these additional factors into the Balance and Gait '*BaG*' scale. Many items of the BaG scale are sensitive to levodopa state and correlate with laboratory measures postural stability[11].

Self-efficacy measures of balance were recorded to better understand the lifestyle implications of DBS. The Activities-specific Balance Confidence (ABC) scale[12] correlates with postural stability[13], gait[14] and falls in PD populations[15]. The Activities of Daily Living (ADL - UPDRS Part II) relates to severity of disease[16] and fear of falling[17]. In this study, by measuring the BaG and self-efficacy scales in addition to the PIGD, a more comprehensive picture of the balance changes with DBS was revealed. The first aim was to determine whether STN or GPi DBS had different effects on balance. The second aim was to determine how postural control is affected by combining the therapies by testing before and after surgery under combinations of medication and DBS.

## METHODS

DBS site was randomized to GPi (n=14) or STN (n=14) and blinded to subjects and experimenters. Natural disease progression was measured in a group of 9 PD control subjects who were eligible for, but chose not to have surgery. Characteristics did not differ among groups (Table 1). Oregon Health & Science University and Portland Veterans Administration Medical Center Institutional Review Boards approved the protocol.

### Protocol

**Baseline—**Subjects reported to the laboratory having withheld their antiparkinsonian medication for at least 12 hours. After initial testing (*OFF* state) subjects took their

medication and were retested after one hour (*ON* state). The baseline visit took place less than a month before DBS surgery.

**Six Months—**Subjects who underwent DBS surgery were tested in this order: DBS on with medication off (*DBS*), DBS and medication both off (*OFF/OFF*), medication on with DBS off (*DOPA*), DBS and medication both on (*ON/ON*). Approximately an hour passed between conditions. Control subjects were tested in *OFF* and *ON* medication states with the baseline protocol.

In each condition, the PIGD and BaG scale were assessed. The BaG scale (See Supplementary Material) consists of 9 test items rated from 4 (unable to perform) to 0 (normal) that evaluate balance in PD: 1) forward leaning to the limits of stability, 2) backward leaning to the limits of stability, 3) stand-to-sit, 4) arm swing during gait, 5) turning ability during gait, 6) doorway negotiation during gait, 7) alternate arm and leg hopping in place, 8) walking with a cognitive task, and 9) standing on toes.

The *ABC* scale assessed the level of confidence to accomplish daily tasks in both their typical off and on medication states. The *ADL* questionnaire was administered once at baseline and six month assessments. For surgery details see St George et al. 2012[18].

## Data Analysis

The items of the BaG and PIGD scales were combined with a weighted average into a single balance score. A linear mixed-model was developed with this balance score as the predictor variable, subject as a random-effects factor and 4 fixed factors: site (STN/GPi), DBS (on/off), medication (on/off) and procedure (baseline/6 months)[18,19]. Reported in the results are the contrast tests between factors in the model that compare the a priori effects of interest between STN and GPi sites:

- *Stimulation effect:* Does turning the stimulator on (*DBS*) improve balance compared to the *OFF/OFF* state post-surgery?
- *Combined effect:* Does combining medication and DBS (*ON/ON*) improve balance beyond what either therapy (*DOPA* or *DBS*) provides individually?
- *Therapeutic effect:* Is balance improved in the “best-treated” state post-surgery (*ON/ON*) compared to pre-surgery (*ON*)?
- *Procedural effect:* Does balance change between the off-treatment state pre-surgery (*OFF*) and post-surgery (*OFF/OFF*)?

Changes in the self-efficacy scales and the control group were determined with repeated measures ANOVAs. Pearson correlations between the balance scales and self-efficacy scales were calculated. To determine the extent that the balance scales accounted for the variance in balance self-efficacy, a linear regression analysis with step-wise entry of both PIGD and BaG factors was performed. Statistical analysis was performed using SAS 9.2 (SAS Institute Inc., Cary, NC, USA).

## RESULTS

Scores in each condition for each group are presented in Figure 1. The BaG score was correlated with the PIGD score (0.78, $p<0.01$).

### Stimulation effect

DBS subjects had improved balance scores when the stimulator was turned on, compared to off, post-surgery for both STN ($p<0.01$) and GPi ($p<0.01$) groups, with no group interaction ($p=0.38$).

### Combined effect

Medication improved balance scores within each group pre- ($p<0.01$) and post-surgery ($p<0.01$). The combined effect (*ON/ON*) improved balance more than either medication ($p<0.01$) or DBS alone ($p<0.01$), and there was no group interaction ($p=0.77$).

### Therapeutic effect

DBS subjects had similar balance scores in the best-treated state (*ON/ON*) post-surgery compared to pre-surgery (*ON*, $p=0.42$) with no interaction between groups ($p=0.99$). The balance score of control subjects did not change over 6 months ($p=0.78$).

### Procedural effect

When comparing the *OFF/OFF* state post-surgery to the *OFF* state pre-surgery there was a group interaction ($p=0.048$). The STN group showed a small but non-significant worsening after surgery ($p=0.08$) and the GPi group had a small but non-significant improvement ($p=0.26$).

### Self-efficacy

The GPi group had improved balance confidence post-surgery ($p=0.05$) due to an improvement in off-medication function (*DBS*). Whereas, the STN and control group showed no change in balance confidence ($p=0.93$). ADL scores did not change for any group between baseline and 6-months. BaG and PIGD scores moderately correlated with *ADL* ($R=0.62$ and 0.49 respectively) and *ABC* scores ($R=-0.60$ and -0.49 respectively). The BaG score alone explained 37% of the variance in the ADL score and 35% of the variance in the ABC score and the addition of PIGD into the model did not increase this value.

## DISCUSSION

This randomized, double-blind study showed that STN and GPi DBS have similar effects on the balance and gait of PD subjects. However, there are some indicators that GPi may be preferable over STN in PD patients with stability concerns. The interaction between the DBS group and change in BaG and PIGD scores after surgery in the *OFF/OFF* state reflected an improvement in the GPi group relative to the STN group. A similar pattern in total UPDRS score was seen in a large multi-centre clinical trial[20] which may have been caused by the PIGD components. This may be due to a lesion effect or differences in the electrical current dissipation times between the two sites[21]. The GPi group reported

improved balance confidence after surgery during the times of the day when medication had worn off but DBS remained on. Balance confidence has been shown to be negatively correlated with incidence of falls in PD populations[15] and the large clinical trial showed there were more severe falls in subjects following DBS in STN compared to GPi[20].

Quantitative laboratory studies have identified some differences between STN and GPi sites. The size of in-place postural responses to perturbations are worse after surgery for the STN, but not the GPi,[18] and step velocity in the STN group is worse after surgery than the GPi[26]. These more subtle differences may be factoring into self-efficacy judgements but are not strong enough to be detected by the clinical measures. The only other randomised trial to date found that STN balance function improved more than GPi function[22], however this study had no control group and only reported PIGD function during the off medication state. Further randomised controlled trials will be required before a definitive decision about the most effective DBS site can be made.

Balance and gait are the result of a complex interaction between some dopa-responsive processes (muscle tone, bradykinesia, tremor), in addition to cortical, sub-cortical and reflexive spinal circuits driven by other neurotransmitters[23]. For both stimulation sites, combining DBS and levodopa medication improved balance beyond what either treatment provided alone, suggesting that DBS may affect non-dopaminergic pathways[18,24,25].

Limitations of this study include the small number of subjects, the non-objective outcome measures and the non-randomised order of the conditions. While we tried to match the PD control group with the DBS group, we cannot exclude differences that led the control group to choose against DBS surgery. The fact that medication dose had not decreased in the STN group may indicate that the electrodes were not placed optimally, or that the blinded clinician had a cautious medication reduction approach. However, the similar dose between groups did allow the DBS effects to be better controlled in this study.

In conclusion, this double-blind randomized trial showed that PD subjects' performance on a range of clinical balance assessments was similar in the best-treated states before and after DBS surgery, for both the STN and GPi sites. Varying the testing conditions between off and on levodopa medication, and off and on DBS, showed synergistic improvements when combining medication and DBS suggesting different neural control pathways are involved.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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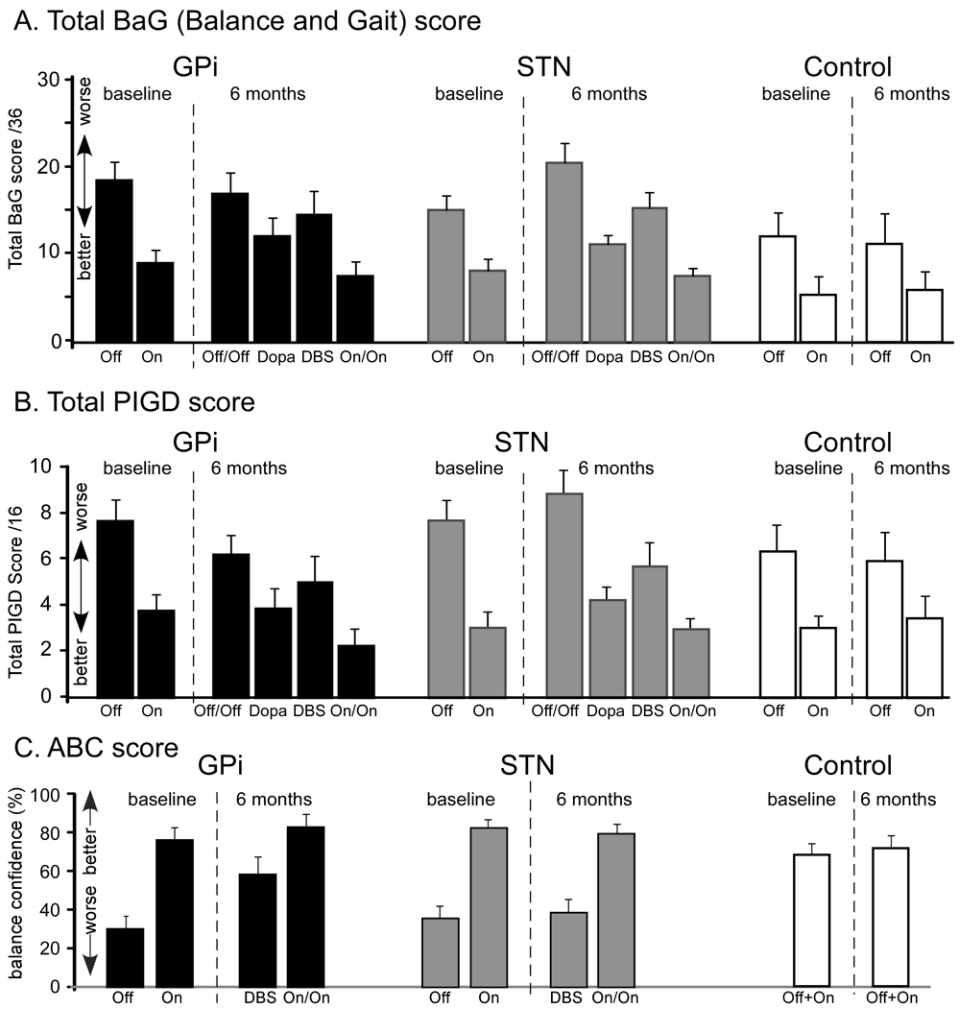


**Figure 1.**

**Table 1**

Characteristics of the PD groups

| | PD-GPi | | PD-STN | | PD Control | |
|---|---|---|---|---|---|---|
| **Age (yrs)** | 61.2 (±9.3) | | 61.0 (±5.7) | | 60.3 (±7.8) | |
| **Gender (% Male)** | 94.4 | | 73.7 | | 78 | |
| **Weight (kg)** | 78.8 (±16.3) | | 80.6 (±19.0) | | 77.4 (±16.1) | |
| **Disease Duration (yrs)** | 13.3 (±6.2) | | 14.5 (±4.8) | | 11.6 (±6.3) | |
| **DBS: voltage V** | 3.6±0.8 | | 3.0±0.9 | | | |
| **frequency Hz** | 174±21 | | 170±22 | | | |
| **pulse width ms** | 98±24 | | 89±25 | | | |
| | **Baseline** | **6m** | **Baseline** | **6m** | **Baseline** | **6m** |
| **Levodopa Equivalent Daily Dose**[27] | 1411 (±844) | 1094 (±348) | 1302 (±681) | 928 (±580) | 1234 (±450) | 1144 (±326) |
| **H&Y Score**† **(OFF)** | 3.8 (±0.9) | 3.4 (±0.7) | 3.5 (±0.8) | 4.0 (±1.2) * | 3.0 (±1.0) | 3.0 (±1.0) |
| **H&Y Score (ON)** | 2.9 † (±0.7) | 2.3† (±0.8) | 2.8† (±1.6) | 2.3† (±0.5) | 2.1† (±0.6) | 2.3† (0.6) |

Standard deviations are shown in parentheses.

*p<0.05 significance compared to control group.

†H&Y: Hoehn and Yahr score[34], the OFF score is off medication at baseline and off both medication and DBS at 6 months, the ON score is on medication at baseline and on both medication and DBS at 6 months.

†p<0.05 significance between H&Y OFF and H&Y ON scores.