# Effect of Subthalamic Deep Brain Stimulation on Posture in Parkinson's Disease: A Blind Computerized Analysis

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**ABSTRACT**

**Introduction.** We sought to assess the effect of subthalamic deep brain stimulation (STN DBS) on Parkinson's disease (PD)-associated postural abnormalities.

**Methods.** A computerized analysis of posture was used to quantify the thoracolumbar, thoracic, and cervical-occipital ventral angles, as well as the thoracolumbar and cervical-occipital lateral angles from the video-repository of three specialized movement disorder centers (n= 158 patients). Data was extracted from frames from video-recordings in the pre-surgical medication-ON (dopaminergic therapy) and post-surgical stimulation-ON/medication-ON states (STN DBS plus dopaminergic therapy). The sum of the five postural angles (global postural angle) was used to compare pre- vs. post-surgical trunk posture alterations. A multivariate analysis was used to examine the association between changes in the postural angles and demographic or clinical variables.

**Results.** There was a 6.7% amelioration in the global postural angle between the pre- and post-surgical assessments (p= 0.031). Motor response to and pre-surgical dosage of levodopa, male gender, and shorter PD duration were identified as predictors for posture improvement after STN DBS. Cases meeting criteria for lower (n= 2) or upper (n= 1) camptocormia respectively improved by 48.1% in the ventral thoracolumbar angle (from 36.4 ± 0.0° to 18.9 ± 4.2°) and 13.8% in the ventral thoracic angle (from 49.1° to 42.3°). Cases meeting criteria for Pisa syndrome (n= 2) improved by 67.5% in the lateral thoracolumbar angle (from 16.9 ± 2.0° to 5.5 ± 4.7°).

**Conclusions.** STN DBS has a relatively small but significant effect on PD-associated postural abnormalities, potentially enhancing the effect of dopaminergic medications alone.

## 1. INTRODUCTION

Abnormal trunk and neck postures are a common cause of functional disability and quality of life impairment in advanced Parkinson's disease (PD) [1-3]. PD-associated posture alterations may range from a "typical" parkinsonian stooped posture, with rounding of the shoulders and flexion of the hips and knees [1], to more severe abnormalities such as antecollis, a non-fixed anterior flexion of the head greater than 45° [4]; camptocormia, an anterior flexion of the spine greater than 30° at the lumbar fulcrum or 45° at the thoracic fulcrum [5]; and Pisa syndrome, a lateral flexion of the trunk greater than 10° that improves with passive mobilization and supine positioning [6].

Therapeutic options currently available for the management of these alterations are limited. Some benefits may be obtained with levodopa or botulinum toxin [1, 7, 8], while neuroleptics, dopamine-agonists, and cholinesterase inhibitors may potentially worsen or even precipitate abnormal postures [1, 9, 10]. Subthalamic nucleus deep brain stimulation (STN DBS) has yielded promising results [11-16]. Still, data related to the efficacy of STN DBS on PD-associated posture alterations remain limited by the lack of clinical scales to assess trunk and neck alterations involving multiple segments of the spine in different axes of space.

We analyzed video-repositories of three specialized movement disorders centers with a computerized system for posture analysis to quantify the effect of STN DBS on trunk and neck postural angles, examine factors associated with response or lack thereof, and correlate the changes detected by computerized video posture analysis with clinical assessment.

## 2. MATERIALS AND METHODS

### 2.1. Study population

We reviewed data from video-repositories collected between 1999 and 2016 in three specialized Movement Disorders Centers (Toronto, Canada; Torino, Italy; and Cincinnati, USA).

2.2. Inclusion and Exclusion Criteria

Inclusion criteria were idiopathic PD as per the UK Brain Bank criteria [17]; bilateral STN DBS; availability of pre- and post-surgical (3-46 months after STN-DBS) video assessments and medical records, including the Unified Parkinson's Disease Rating Scale (UPDRS) [18] or Movement Disorders Society UPDRS (MDS-UPDRS) [19] motor score (section-III) in medication-OFF (Med-OFF) and medication-ON (Med-ON).

Exclusion criteria were severe orthopedic spine disorders (i.e., vertebral fractures, severe osteoporosis, Pott's disease, etc.); history of spine surgery; and clinical features suggesting a diagnosis other than idiopathic PD.

2.3. Video frame extraction and marker placement for posture analysis

We reviewed video-recordings from patients assessed in the pre-surgical medication-ON (defined as a condition of maximal effect of oral dopaminergic medication, at least 45 minutes after the administration of a levodopa dose) and post-surgical medication-ON and stimulation-ON (Stim-ON/Med-ON, defined as a condition of maximal effect of oral dopaminergic medications and STN DBS) to capture the following frames: a) two dorsal views during gait, at left heel contact and at right heel contact during the same gait cycle; and b) two lateral views in static standing (Figure 1).

Frames were encoded for the serial number of the patient, number of frames, and assessment time points (pre- or post-surgical), encrypted to blind for the assessment condition (Med-ON vs. Stim-ON/Med-ON), and analyzed using "ImageJ", an open source image processing

program developed by the National Institute of Health and validated for posture analysis [8, 20].

Marker landmarks were set on each frame following the recent consensus for measurement of the camptocormia angle [5] and previous publications on frame-based postural assessments in PD-patients [8, 15, 20-22], as follows (Figure 1):

- M1-M3: calibration markers used to calculate camera rotation and set at points in the room forming lines at 90˚ angles in the horizontal and vertical planes (e.g., corner of the wall).
- M4: Occipital protuberance
- M5: Spinous process of the seventh cervical vertebra
- M6: Spinous process of the fifth lumbar vertebra
- M7: 1/3 of the distance between M5 and M6
- M8: 2/3 of the distance between M5 and M6
- M9: Lateral malleolus

Output files were processed using a custom script for MATLAB (R2015b) to correct for camera rotation (Supplementary material), excluding frames with adverse camera positioning and calculating the following angles: ventral thoracolumbar (180° minus the angle between the lines connecting M6 to M9 and M5 to M6), ventral thoracic (180° minus the angle between the lines connecting M5 to M7 and M6 to M7), ventral cervical-occipital (angle between the lines connecting M4 to M5 and M5 to M6), lateral thoracolumbar (angle between the line connecting M5 to M6 and the vertical line), and lateral cervical-occipital (angle between the lines connecting M5 to M6 and M4 to M5) [21, 23].

2.4. Study Aims and Outcome Measures

The primary endpoint was the global postural angle calculated by the sum of the ventral thoracolumbar, ventral thoracic, ventral cervical-occipital, lateral thoracolumbar, and lateral cervical-occipital postural angles. We also evaluated whether (a) changes on trunk posture alterations were associated with selected demographic and clinical variables (age at PD onset and at surgery; PD duration; motor symptom severity; motor response to the levodopa challenge test; and changes in Levodopa Equivalent Daily Dose (LEDD) [24]; and (b) changes on computerized video analysis were correlated with a clinical evaluation using a scale of 0 to 4, as per the UPDRS scoring system [25]. Further, we evaluated potential associations between individual changes in the postural angles and clinical/demographic characteristics. Antecollis, Pisa syndrome, and camptocormia were defined as per the recent consensus definitions as follows: ventral cervical-occipital angle > 45° (antecollis) [4], lateral thoracolumbar angle > 10° (Pisa syndrome) [6], and ventral thoracolumbar angle > 30° or ventral thoracic angle > 45° (camptocormia) [5].

2.6 Statistical analysis

Demographic and clinical data were described with appropriate summary measures (mean ± standard deviation for continuous variables and frequency for dichotomous variables). Changes in the global postural angle, in the single postural angles, and in the clinical posture score between the pre- and post-surgical assessments were analyzed using a two-tailed paired t-test or the non-parametric Wilcoxon signed-rank test, as appropriate. Data distribution was tested using the Kolmogorov-Smirnov-Test. A multivariate linear regression analysis was used to evaluate the association between clinical/demographic characteristics and the extent of STN DBS response on trunk postural alterations using, as dependent variables, the percentage changes (pre- vs. post-surgical evaluation) of the global postural angle and single postural angles. Independent variables included age at surgery, PD duration at surgery, pre-surgical

motor score (UPDRS part III) in Med-OFF, relative response to levodopa [(UPDRS part III Med-OFF – UPDRS part III Med-ON) x 100 / UPDRS part III Med-OFF]], levodopa-LEDD, dopamine agonist-LEDD, and LEDD reduction after surgery. Gender was included as a binary variable (m= 0, f= 1). A validated formula [25] was used to convert MDS-UPDRS into UPDRS scores, when needed. The Spearman's correlation test was used to estimate the correlation between the global postural angle (and related postural angles) and the clinical posture score. When available, the following data were extracted from clinical records: use of amantadine, catechol-O-methyltransferase (COMT)-Inhibitors, and monoamine oxidase B (MAO-B)-Inhibitors; STN DBS contact levels (0-3, being 0 the more ventral contact), stimulation intensity (average between left and right side), stimulation frequency (Hz), pulse width (μsec), and asymmetry of stimulation (stimulation intensity in the left electrode minus stimulation intensity in the right electrode).

All p-values reported are two-tailed, with a level of significance of 0.05. Significance-levels were adjusted in the multivariate linear regression model using the Benjamini-Hochberg-Procedure to account for multiple testing. Missing values were excluded from the analysis. Data were analyzed using the Statistical Package for the Social Sciences 25.0 for Windows (SPSS, Chicago, IL).

## 3. RESULTS

A total of 158 patients, including three cases of camptocormia (two involving the lower spine and one involving the upper spine) and two of Pisa syndrome, met all of the inclusion and none of the exclusion criteria and were included in the analyses (Table 1). Pre-surgical data were compared to a post-surgical follow-up of 15.4 ± 11.0 months.

### 3.1 STN DBS effect on posture

The global postural angle improved by 6.7% between the pre-surgical and post-surgical assessments, from 53.8 ± 21.6° [range 2.4 - 116.5] to 50.2 ± 17.2° [range 13.9 – 100.0] (p= 0.031) (Figure 2). Patients with lower (n= 2) and upper (n= 1) camptocormia respectively improved by 48.1% in the ventral thoracolumbar angle (36.4 ± 0.0° to 18.9 ± 4.2°) and 13.8% in the ventral thoracic angle (49.1° to 42.3°). Patients with Pisa syndrome (n= 2) improved by 67.5% in the lateral thoracolumbar angle (16.9 ± 2.0° to 5.5 ± 4.7°). There were no patients meeting the criteria for camptocormia or Pisa syndrome at the postoperative assessment. The clinical posture score showed a trend towards improvement after STN-DBS (12.9%; from 1.1 ± 0.8 to 0.9 ± 0.8; p= 0.082).

3.2 Factors associated with STN DBS effect

Gender, age, PD duration, LEDD, and motor response at the pre-surgical levodopa test explained 37% of the global postural angle post-surgical change (R= 0.72, p= 0.006) (Table 2), with low pre-surgical motor response to levodopa being the strongest predictor of improvement (Beta= -0.67, p< 0.001). In the analysis of single angles, the model indicated a correlation between the following factors:

a) Improvement (decrease) in the ventral thoracolumbar angle and 1) pre-surgical levodopa-LEDD (Beta = -0.61, p< 0.001), and 2) pre-surgical motor response at the levodopa test (Beta = -0.54, p< 0.001).

b) Improvement (decrease) in the ventral thoracic angle and male gender (Beta= -0.54, p= 0.002)

c) Improvement (decrease) in the lateral cervical-occipital angle and PD duration (Beta= 0.50, p= 0.001) (Table 2).

There was low collinearity between variables at the multivariate analysis (Variance-inflating-factor < 2).

3.3 Correlation between clinical rating and postural scores

The clinical posture score correlated with the global postural angle (rho= 0.27; $p < 0.001$), the ventral thoracolumbar angle (rho= 0.28; $p < 0.001$), the ventral thoracic angle (rho= 0.19; p= 0.005), and the lateral cervical-occipital angle (rho= 0.18; p= 0.006). No correlations were found with the remaining postural angles.

## 4. DISCUSSION

Using a blind computerized approach, we evaluated the effect of STN DBS on trunk and neck posture alterations in a large cohort of PD patients, finding an average improvement of 6.7% in the overall sample and a substantial amelioration in patients with camptocormia or Pisa syndrome.

Previous studies reported promising but not definitive results for postural amelioration with STN DBS [11], with a correlation between STN DBS efficacy and shorter duration of symptoms [16], and at least partial response to levodopa [13]. It is likely that the small sample size and the absence of standardized scales for the assessment of trunk and neck posture alterations contributed to the heterogeneity of clinical outcomes described in previous reports [12]. We, therefore, opted for employing an objective quantitative measure to study a large multi-center cohort of PD patients treated with STN-DBS.

This study has the major innovation of assessing the entire spectrum of PD-associated postural alterations using a quantitative and objective method. Significant correlations with the clinical posture assessment demonstrated the validity of this tool to quantify posture alterations, and the analysis of consecutive patients provided a global index of STN DBS efficacy on trunk and neck postures. It should be considered, on the other hand, that the

inclusion of consecutive patients, including those with no or minimal postural impairment, might have partially diluted the final results in terms of percentage improvement.

Multiple features emerged as possibly modulating the effect of STN DBS on individual postural angles. Male gender was identified as a predictor of STN DBS improvement in upper camptocormia, with a trend towards greater improvement also in lower camptocormia and global postural angle. Age and PD duration at the time of surgery were identified as possible predictors for posture improvements on the frontal plane. In particular, PD duration correlated to the improvement in the lateral cervical occipital angle and younger age to the improvement in the lateral thoracolumbar angle. Motor response to and pre-surgical dosage of levodopa showed an inverse correlation with the ventral thoracolumbar angle, suggesting a differential effect of STN DBS and dopaminergic medications on thoracolumbar posture abnormalities. Also, a post-surgical reduction in dopamine agonist correlated with lateral and ventral thoracolumbar angle improvement. This last finding seems to confirm the notion that dopamine agonists may have a detrimental effect on postural alterations [3, 5, 26].

The strength of our results should be tempered by some limitations. First, the lack of information related to the duration of posture abnormalities, which may play a crucial role in the outcome of STN DBS, as previously reported by other authors [16]. Second, the short follow-up, with lack of data on the long-term posture effect of STN DBS. Third, the lack of patient-centered measures of functional impairment such as health-related quality of life. Fourth, the retrospective study design did not allow a thorough assessment of mild spine disease or functional posture alterations associated with back pain. Finally, the fluctuating nature of PD-associated postural alterations could have influenced the measurement of posture in the clinical setting.

Taking into account the possible biases associated with these limitations, our findings indicate that STN DBS has a small but significant effect on trunk and neck postural alterations, potentially enhancing the effect of dopaminergic therapy alone. Further research using an objective methodology similar to the one employed in this study is needed to determine the long-term effects of STN DBS, clarify whether an early surgical treatment may prevent the development of disabling trunk posture abnormalities in PD, and confirm the importance of clinical and demographic predictors on the STN DBS postural outcome.

**Authors' Roles:**

Jan Roediger: study design, analysis and interpretation of data, drafting of the manuscript.

Carlo Alberto Artusi: study design, interpretation of data, drafting of the manuscript.

Alberto Romagnolo: critical revision of manuscript for intellectual content, revision of the statistical analysis.

Pierce Boyne: interpretation of data, critical revision of manuscript for intellectual content.

Maurizio Zibetti: critical revision of manuscript for intellectual content.

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Alberto J. Espay: interpretation of data, critical revision of manuscript for intellectual content.

Alfonso Fasano: study concept and design, interpretation of data, critical revision of manuscript for intellectual content, revision of the statistical analysis.

Aristide Merola: study concept and design, interpretation of data, critical revision of manuscript for intellectual content, revision of the statistical analysis.

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**Table 1. Demographic and clinical data**

| Pre-surgical assessment | |
|---|---|
| **Age at PD onset (years)** | 46.2 ± 8.4 (20 - 67) |
| **Age at DBS-Surgery (years)** | 58.7 ± 7.7 (38 - 76) |
| **PD Duration at DBS-Surgery (years)** | 11.8 ± 4.7 (4 - 29) |
| **LEDD total (mg)** | 1484 ± 632 (250 - 3080) |
| **LEDD for Levodopa only (mg)** | 1256 ± 637 (225 - 2793) |
| **LEDD for Dopamine agonists (mg)** | 172 ± 196 (0 - 1000) |
| **Amantadine use (%)** | 40.2 |
| **COMT Inhibitors use (%)** | 36.8 |
| **MAO-B Inhibitors use (%)** | 21.8 |
| **UPDRS-III Total – Med-OFF** | 46.8 ± 13.5 (18 – 93) |
| **UPDRS-III Total – Med-ON** | 19.6 ± 8.5 (3 - 47) |
| **Post-surgical assessment** | |
| **UPDRS-III Total – Med-ON/Stim-ON** | 25.4 ± 12.2 (5 - 67) |
| **LEDD for Levodopa only (mg)** | 807 ± 516 (0 - 2400) |
| **LEDD for Dopamine agonists (mg)** | 38 ± 74 (0 - 320) |
| **LEDD total (mg)** | 879 ± 511.0 (0 - 2580) |
| **Amantadine use (%)** | 11.8 |
| **COMT Inhibitors use (%)** | 4.7 |
| **MAO-B Inhibitors use (%)** | 9.4 |
| **STN DBS contact levels (%) right** | 0 : 2<br>1 : 29<br>2 : 47<br>3 : 22 |
| **STN DBS contact levels (%) left** | 0 : 3<br>1 : 23<br>2 : 50<br>3 : 24 |
| **STN DBS stimulation amplitude (V)** | 3.2 ± 0.6 (1.5 - 5.1) |
| **STN DBS stimulation frequency (Hz)** | 137 ± 31 (60 - 210) |
| **STN DBS stimulation pulse width (µs)** | 61 ± 4 (60 - 90) |

| | |
|---|---|
| **STN DBS stimulation asymmetry (V)** | 0.4 ± 0.5 (0 - 2.5) |

Abbreviations: PD: Parkinson's disease; DBS: Deep brain stimulation; LEDD: Levodopa equivalent daily dose; COMT: Catechol-O-methyltransferase; MAO-B: monoamine oxidase B; UPDRS: Unified Parkinson's Disease Rating Scale; STN: subthalamic nucleus.

**Table 2. Clinical and demographic predictors of STN DBS response on trunk and neck postural angles**

| Demographic and clinical variables | Global postural angle | Ventral thoracolumbar angle | Ventral thoracic angle | Ventral cervical-occipital angle | Lateral thoracolumbar angle | Lateral cervical-occipital angle |
|---|---|---|---|---|---|---|
| **Gender** | -0.39 | -0.22 | **-0.54*** | 0.10 | 0.05 | 0.06 |
| **Age at DBS-Implantation** | -0.09 | -0.18 | -0.08 | 0.07 | -0.28 | -0.10 |
| **PD Duration at DBS-Implantation** | 0.18 | -0.18 | 0.03 | 0.05 | 0.19 | **0.50*** |
| **Pre-surgical levodopa-LEDD** | -0.41 | **-0.61*** | -0.34 | -0.03 | 0.16 | 0.02 |
| **Pre-surgical dopamine agonists-LEDD** | 0.19 | 0.16 | 0.02 | -0.27 | -0.12 | 0.03 |
| **Pre-surgical UPDRS-III – Med-OFF** | 0.20 | 0.30 | 0.30 | -0.05 | 0.06 | -0.02 |
| **Pre-surgical motor response to levodopa** | **-0.67*** | **-0.54*** | -0.33 | 0.05 | -0.22 | 0.02 |
| **Post-surgical levodopa-LEDD reduction** | 0.09 | 0.01 | -0.18 | 0.24 | -0.13 | 0.17 |
| **Post-surgical dopamine agonists-LEDD reduction** | 0.11 | 0.18 | 0.05 | 0.06 | 0.20 | -0.08 |
| **Adjusted R-Squared** | **0.37*** | **0.25*** | 0.14 | -0.08 | -0.01 | 0.13 |

Results of the Multiple linear regression models with post-surgical improvement of postural angles as dependent variables. Standardized Beta coefficients shown for the independent

variables. Last row displays the models overall adjusted-R-Squared as a measure for predictive power.

Abbreviations: * = Benjamini-Hochberg adjusted p-value <0.05; PD: Parkinson's disease; DBS: Deep brain stimulation; LEDD: Levodopa equivalent daily dose; UPDRS: Unified Parkinson's Disease Rating Scale.

**Figure 1. Measurement of postural scores**

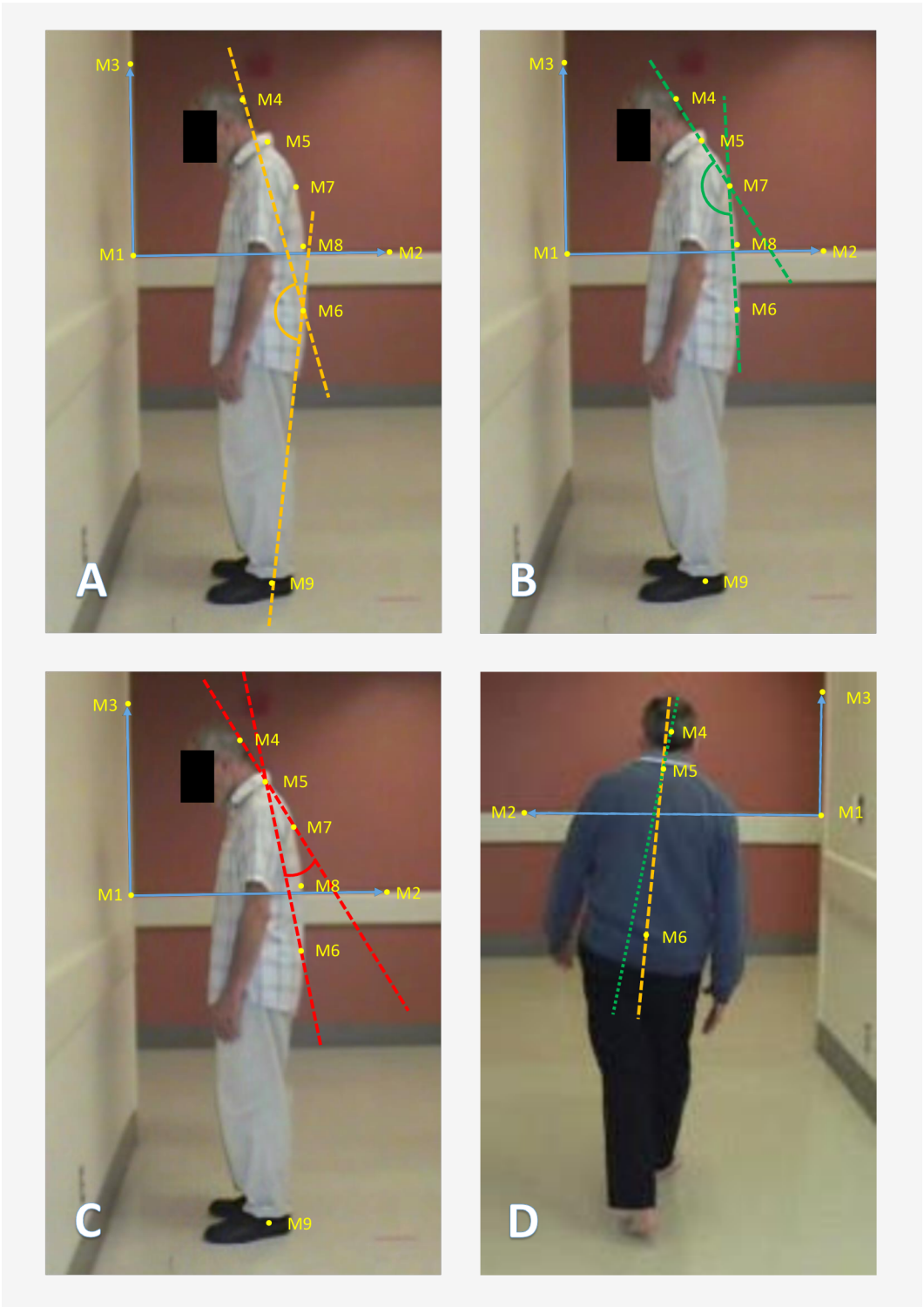

**Figure 2. Boxplots of pre- and post-DBS postural angles**

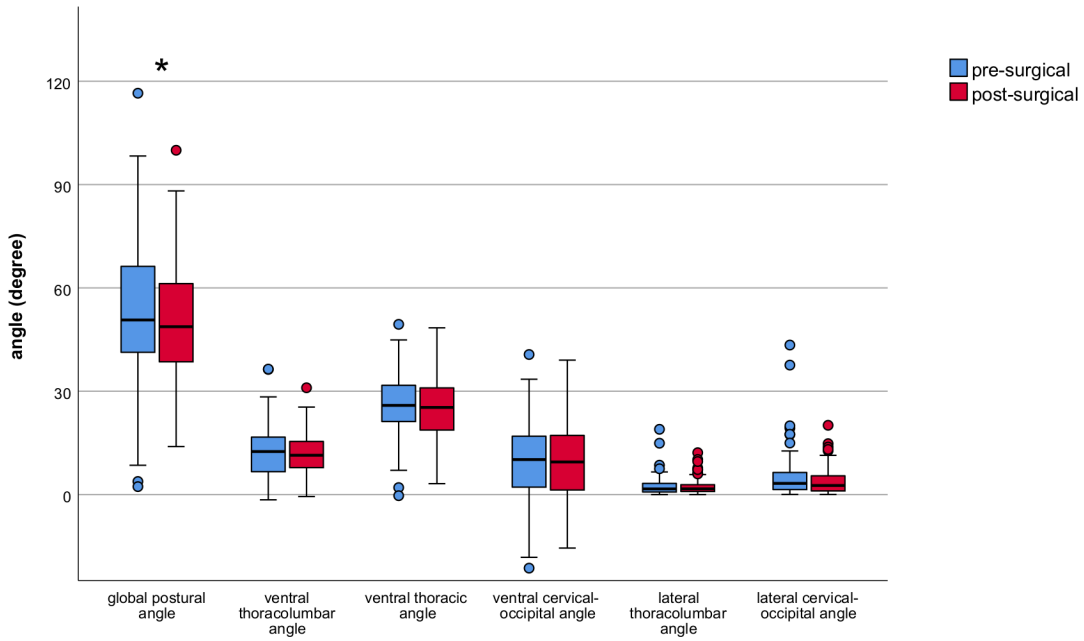

**Figure captions**

**Figure 1 - Measurement of postural scores**

A) Ventral thoracolumbar angle: 180° minus the angle between the line passing through M9 (lateral malleolus) and M6 (L5 spinous process) and the line between M6 (L5) and M5 (C7 spinous process); B) Ventral thoracic angle, defined as 180° minus the angle between the vector M7-M5 and M7-M6 (1/3rd of the distance between C7 and L5 to C7 and to L5); C) Ventral cervical-occipital angle, measured as the angle between the vector M4-M5 (occipital protuberance to C7) and the vector M5-M6 (C7 to L5); D) Angles in dorsal view measured as absolute values between the vector M5-M6 (C7 to L5 - green) and the vertical line (lateral thoracolumbar angle) and between the vector M5-M6 (green) and M5-M4 (C7 to occipital protuberance - red: lateral cervical-occipital angle). Landmarks M1-M3 were set identifying a point in the room close to the patient, which has a 90˚ angle, for calculating the camera rotation.

**Figure 2 - Boxplots of pre- and post-DBS postural angles**

Boxplots of global postural angle and single postural angles at the pre-surgical (blue bars) and post-surgical (red bars) evaluation. Abbreviations: * = $p < 0.05$