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THE EFFECT OF DEEP BRAIN STIMULATION ON GAIT AND POSTURE DISORDERS IN PATIENTS WITH PARKINSON'S DISEASE

321.05. CLINICAL NEUROLOGY

Summary of Ph.D. Thesis in Medical Sciences

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The thesis was developed in the Scientific Laboratory of Functional Neurology of the Institute of Neurology and Neurosurgery "Diomid Gherman" in co-supervision with the Department of Neurology, Christian-Albrechts University, Campus Kiel, Germany.

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The presentation will take place on 17.05.2023, at 14:00, in the premises of USMF "Nicolae Testemitanu", bd. Ștefan cel Mare și Sfânt, 165, office 205 in the meeting of the Commission for the public defense of the PhD thesis, approved by the decision of the Scientific Council of the Consortium of 01.12.2022.

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CONCEPTUAL RESEARCH MILESTONES

The importance of the topic: Neurological disorders are the leading cause of disability and the second leading cause of death globally [1]. Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease. The incidence of PD is similar worldwide, with 13-23.8 new cases reported per 100,000 population per year [2]. For reasons that are not yet fully understood, the incidence and prevalence of this disease have increased rapidly over the last two decades [3].

BP is a chronic, progressive, and disabling condition caused by neuronal loss of the substantia nigra, resulting in a deficiency of striatal dopamine. Current criteria define Parkinson's disease as the presence of bradykinesia combined with either rest tremor, rigidity, or both. However, the clinical presentation is multifaceted and includes many non-motor symptoms.

Axial motor aspects including gait disturbances and postural abnormalities are common in patients with BP, so that on average 10-15 years after diagnosis, axial signs dominate the motor picture [4]. Axial motor symptoms can be extremely debilitating, the best example being gait freezing, which episodically impairs patients' ability to generate efficient forward movements [5]. Other axial signs that significantly affect independence and quality of life include postural alignment changes such as camptocormia and Pisa syndrome [6].

Axial motor features are often largely resistant to dopamine replacement therapy. Subthalamic nucleus deep brain stimulation (STN-DBS) is an already well-established procedure for the symptomatic treatment of BP. Although long-term data are available for STN-DBS, definitive evidence for the management of axial disability is still lacking at present [7]. In clinical practice the treatment of axial disorders by STN-DBS remains challenging. Axial characteristics may improve in some patients, remain unchanged in others or even worsen in some as an effect of the intervention [8]. In this study we aimed to analyse the phenomenon of gait freezing and postural disorders in the preoperative and postoperative phase of STN-DBS to support clinicians in the complex decision of whether or not to offer STN-DBS as a treatment option to each individual patient.

The typical pathological manifestations of Parkinson's disease considerably affect the gait and posture patterns of patients. As the disease progresses these problems worsen and represent a major burden of disease that significantly affects independence and quality of life. Although dopaminergic drugs improve certain aspects of gait such as speed and stride length, episodic symptoms such as freezing of gait have a much more variable response to treatment. For this reason, in this study we focused on detailed study of episodic gait phenomena, particularly freezing of gait. Approximately 1/3 of patients with BP exhibit abnormal gait. A large number of patients have severe postural abnormalities such as camptocormia and Pisa syndrome. Diagnosis and management of these severe postural deformities remains difficult, therefore in this paper we aimed to investigate camptocormia and Pisa syndrome.

The STN-DBS method, which appeared 30 years ago, was enthusiastically conceived as an alternative treatment for BP. Although this method is already a well-established treatment for cardinal motor symptoms of BP [9] its effects on axial symptoms, such as gait and postural disorders, are controversial and not fully elucidated.

One of the major reasons for different and conflicting results is the complexity of the clinical phenomenology of freezing gait and postural disorders, both aspects of the disease being difficult to assess. Thus, the basic aim of this study was to objectively assess the phenomenon of gait freezing by detailed analysis of a video-recorded gait task, and postural disorders by using an app that accurately identifies the angle of postural deviation. Patients were investigated before and after the STN-DBS intervention, and the results were used to analyze the efficacy of STN-DBS for the treatment of the mentioned axial symptoms.

The aim of this study was to evaluate the effect of deep brain stimulation of the subthalamic nucleus on freezing gait, camptocormia and Pisa syndrome in patients with Parkinson's disease in order to develop an algorithm for selecting eligible candidates for this intervention.

Research objectives:

1. To assess the frequency and severity of gait freezing in patients with Parkinson's disease and to identify the most sensitive circumstances for causing gait freezing during a standardized gait task.
2. To identify an objective clinical test with the highest predictive value for estimating improvement of gait freezing in patients with Parkinson's disease following subthalamic nucleus deep brain stimulation intervention.
3. Analysis of types of turning strategies in patients with Parkinson's disease and their correlation with severity of motor impairment.
4. To determine the efficacy of subthalamic nucleus deep brain stimulation intervention for the treatment of gait freezing in patients with Parkinson's disease.
5. Characterization of postural alignment in patients with Parkinson's disease, i.e., anterior tilt differentiated into total camptocormia and superior camptocormia, and lateral tilt, referred to as the "Pisa angle" using a standardized digital instrument (NeuroPostureApp).
6. Investigating the effect of deep brain stimulation of the subthalamic nucleus on postural alignment in patients with Parkinson's disease.

Research hypothesis: Subthalamic nucleus deep brain stimulation (STN-DBS) intervention reduces the severity of gait freezing, camptocormia and Pisa syndrome in patients with Parkinson's disease.

Summary of thesis sections: The thesis consists of an Introduction, four chapters, general conclusions, and practical recommendations. The thesis consists of 100 pages of basic text and includes 6 tables and 13 figures. The bibliography in the paper includes 194 relevant sources in the field of medical research. These have been used to argue and support the statements in the paper. Finally, we have included three appendices, which contain additional data on the patient cases investigated.

In the **Introduction** chapter we highlight the importance and topicality of issues related to gait and posture disorders in patients with Parkinson's disease. To this end, we briefly reviewed relevant worldwide epidemiological data, risk factors, etiopathogenic hypotheses of the disease and current treatment options. We also assessed the impact of deep brain stimulation of the subthalamic nucleus on these symptoms.

In **Chapter** 1, contemporary concepts related to gait and postural disorders in patients with Parkinson's disease and available treatment options are presented. We have made a structured synthesis of data from the literature, highlighting the achievements and problems of the research field. We presented worldwide epidemiological data on the phenomenon of gait freezing, camptocormia and Pisa syndrome in patients with Parkinson's disease, risk factors and etiopathogenic hypotheses of the disease based on contemporary scientific support. In addition, we describe in detail the current information on the effect of deep brain stimulation of the subthalamic nucleus on these symptoms. This has been addressed using relevant studies from the recent literature.

In **Chapter 2** we described the methodology and research design. The arrangements of the research protocol were outlined, including the criteria for patient selection and the principles according to which patients were monitored pre- and postoperatively. We also described in detail the methods of analysing gait freezing, postural angles and statistical data processing.

In **Chapter 3** the results of research on the impact of deep brain stimulation of the subthalamic nucleus on gait freezing in patients with Parkinson's disease were presented in detail. Thus, the frequency and severity of the symptom before and after surgery were presented using various assessment and measurement tools. To illustrate these issues more clearly, graphs and tables were used to clearly show the differences between patients' condition before and after deep brain stimulation. Detailed statistical analyses have also been presented and performed to compare data and assess the effectiveness of the treatment.
Chapter 4 is devoted to presenting the results of the evaluation of postural disorders, namely camptocormia and Pisa syndrome, in Parkinson's disease patients following subthalamic nucleus deep brain stimulation intervention. Statistical analysis of the data, performed to assess the efficacy of subthalamic nucleus deep brain stimulation intervention in improving postural disorders in patients with Parkinson's disease, is described.
Chapter 5 contains the interpretation and analysis of the results obtained from the research, with reference to the literature and the original aims and hypotheses of the study. Implications and limitations of the research are addressed and discussed, as well as possibilities for future research and development in this area. Research contributions to the treatment and care of patients with Parkinson's disease and gait and posture disorders are also highlighted.
The thesis concludes with **General Conclusions** and **Practical Recommendations.**

Overall research methodology: To achieve the proposed objectives, the study was conducted as an observational-analytical, retrospective and prospective cohort research. The research was approved by the Research Ethics Committee of the State University of Medicine and Pharmacy "Nicolae Testemitanu" (verbal process no. 44/53 of 12.04.2018). A total of 192 patients with idiopathic Parkinson's disease who underwent deep brain stimulation of the subthalamic nucleus (STN-DBS) were included in the study. To assess the phenomenon of gait freezing we used a scale based on the clinical pattern of gait freezing in different challenging situations based on video analysis of a standard gait sample. Regarding postural disorders, patients were characterized depending on their anterior tilt, differentiated into total camptocormia (TCC) and upper camptocormia (UCC), as well as lateral tilt, referred to as "Pisa angle". Postural disturbance testing was assessed using photographs captured from standardized gait task videos and angles were calculated using the NeuroPostureApp ©, which was developed and validated by our team. To investigate the effect of STN-DBS the results were compared in two pre-operative medical conditions (OFF-medication and ON-medication) and four post-operative medical conditions (ON-medication/OFF-stimulation, ON-medication/ON-stimulation, OFF-medication/OFF-stimulation and OFF-medication/ON-stimulation), thus each patient is their own control before and after STN-DBS intervention. Statistical analysis was performed using R statistical analysis software (version 1.0.136).

Approval of scientific results: The results of the study were published in 6 original articles in journals with impact factor (1 article in a journal with impact factor 5.1, 3 articles in journals with impact factor 4.3, 1 article in a journal with impact factor 3.9 and 1 article in a journal with impact factor 2.7), the author being first author in 4 of the papers. Scientific results were also published in 2 national category B journals.
The work has been presented and discussed at international and national scientific conferences, such as:
- International Congress of the Parkinson's Disease and Other Movement Disorders Society (Philadelphia-virtual, 2020; Nice, 2019).
- Congress of the European Academy of Neurology (Paris-virtual 2020)
- Congress of the Society for Functional and Stereotactic Neurosurgery (New York, 2019)
- First Parkinson's Disease Congress in Romania (Brasov-virtual, 2020)

- Annual Congress dedicated to the anniversary of USMF "Nicolae Testemitanu" (Chisinau 2019, Chisinau 2020)
- MedEspera Congress (Chisinau, 2020).

Keywords: Parkinson's disease, STN-DBS, L-DOPA, gait freezing, postural disorders, camptocormia, Pisa syndrome.

THESIS CONTENT

1. Contemporary concepts of prevalence, pathogenesis, clinical phenotypes and treatment options for gait and posture disorders in patients with Parkinson's disease.

In the given section a thorough review and synthesis of current publications related to the subject of the thesis are presented with reference to the etiopathogenesis, diagnosis and treatment of gait and posture disorders in patients with Parkinson's disease. At the same time, a detailed analysis of similar studies on the effect of deep brain stimulation of the subthalamic nucleus in patients with Parkinson's disease was performed.

2. Research materials and methods.

An analytical, observational, prospective cohort study was conducted to follow the effect of deep brain stimulation on gait and posture disorders in patients with Parkinson's disease. Patients with idiopathic Parkinson's disease (PD) who underwent subthalamic nucleus deep brain stimulation (STN-DBS) surgery and met inclusion and exclusion criteria were included. The research was developed within the Scientific Laboratory of Functional Neurology of the Diomid Gherman Institute of Neurology and Neurosurgery in collaboration with the Department of Neurology and Neurosurgery of the Christian-Albrechts University of Kiel, Germany.

A total number of 344 patients with idiopathic BP operated STN-DBS were enrolled in the study, as 152 patients did not show up during the first year for the follow-up visit they were excluded from the study. Respectively, we included 192 BP patients for the investigation of postural disorders; for the study of gait freezing only those patients who presented with gait freezing (n=124) at the interview that took place at the baseline visit were selected from these patients.

Inclusion criteria for the study were: (1) signing the consent agreement to participate in the research; (2) adult age (greater than or equal to 18 years), (3) Parkinson's disease as determined by the UK Brain Bank clinical criteria; (4) undergoing the bilateral electrode implantation procedure for deep brain stimulation of the subthalamic nucleus; (5) performing the L-DOPA test with video recording of the UPDRS III scale (motor examination part) before electrode implantation and at the first follow-up visit, performed at 6-24 months post-operatively, in all 4 possible conditions after stimulation (ON-medication/OFF-stimulation, ON-medication/ON-stimulation, OFF-medication/OFF-stimulation and OFF-medication/ON-stimulation); (6) only patients with item no. 14 (gait freezing) of section II of the UPDRS scale greater than or equal to 1 pre-operatively.

Exclusion criteria for the study were: (1) lack of consent to participate in the research; (2) minors under 18 years of age; (3) presence of Parkinson's disease in first-degree relatives; (4) presence of other diseases that might have affected the patients' gait and posture.

Surgical technique. In all cases, a Leksell®-G stereotactic frame (Elekta Instruments AB, Stockholm, Sweden) was mounted on the patient's head under local anaesthesia. A 1.5T MRI scanner (Genesis Signa, GE Medical Systems) was used for preoperative planning. STN was localized by a combination of MRI, microelectrode recording (MER). A multi-channel parallel probe (four or five channels, so-called "Ben Gun") was used for MER and stimulation. Chronic quadripolar electrodes (DBS 3389, Medtronic or Boston Scientific) were implanted with

local anesthesia and IPGs were then implanted subcutaneously with general anesthesia in a single operation. Patients underwent computed tomography (CT) scanning (64-channel Brilliance CT, Philips, Eindhoven, The Netherlands) immediately after the DBS operation. Video recording of the standardized L-DOPA test. STN-DBS intervention in BP patients was considered in patients with good dopamine response. To determine responsiveness to dopaminergic drugs, pre-operatively the patient was assessed UPDRS, in the "OFF" state (no drug), then in the "ON" state (after administration of 1.5 of the usual dose of L-DOPA). A 30% decrease in the UPDRS motor part (UPDRS-III) was considered sufficient to recommend surgery.

Video recording of the standardized L-DOPA test. STN-DBS intervention in patients with BP was considered in patients with good dopamine response. To determine responsiveness to dopaminergic drugs, pre-operatively the patient was assessed UPDRS, in the "OFF" state (no drug), then in the "ON" state (after administration of 1.5 of the usual dose of L-DOPA). A 30% decrease in the UPDRS motor part (UPDRS-III) was considered sufficient to recommend surgery.

Method of assessment of gait freezing phenomenon. A total of 124 patients, 744 video sequences, each patient was evaluated and videotaped 6 times, 2 pre-operative and 4 post-operative situations, as described above, were examined for the investigation of gait freezing phenomenon. Clinical patterns were used to classify the severity of gait freezing on a scale from 0 to 3 as follows: 0 - no gait freezing;1 - forward sliding with small steps (engl., shuffling forward with small steps; 2 - trembling in place with alternating, rapid knee movements; 3 - complete akinesia without limbs or trunk movement. Challenging situations: the frequency and severity of gait freezing were assessed in various situations, which could precipitate gait freezing sequences: (1) initiating gait; (2) turning 180o; (3) walking in open space and (4) reaching a destination (chair/camera floor). The total severity score is the arithmetic sum of the severity score for the 4 challenging circumstances.

The turning strategies in this study were classified into three categories: the pivot/spin strategy, referred to as "spin": turning on one or both legs simultaneously, the change of direction is performed in one movement;the "step" strategy: the change of direction to 180 is performed with 3 steps or more, no pivoting takes place;the mixed strategy (pivot plus step): the turn is performed with 1-3 steps and a pivot. The identification of the preferred strategy was based on video recordings that were reviewed by two "blind" assessors who had no information about the treatment condition.

Postural disorder assessment method. Two angles for lateral deviation were determined, the total angle and the upper camptocorm angle, as well as the lateral deviation angle, called the Pisa angle (Figure 1). The NeuroPostureApp © (http: //www.neuroimaging.uni-kiel.de/NeuroPostureApp), which was developed in Kiel in 2018 for this purpose by a team of IT technicians and neurologists, was used. The evaluators were provisionally trained based on 100 randomly chosen photos.

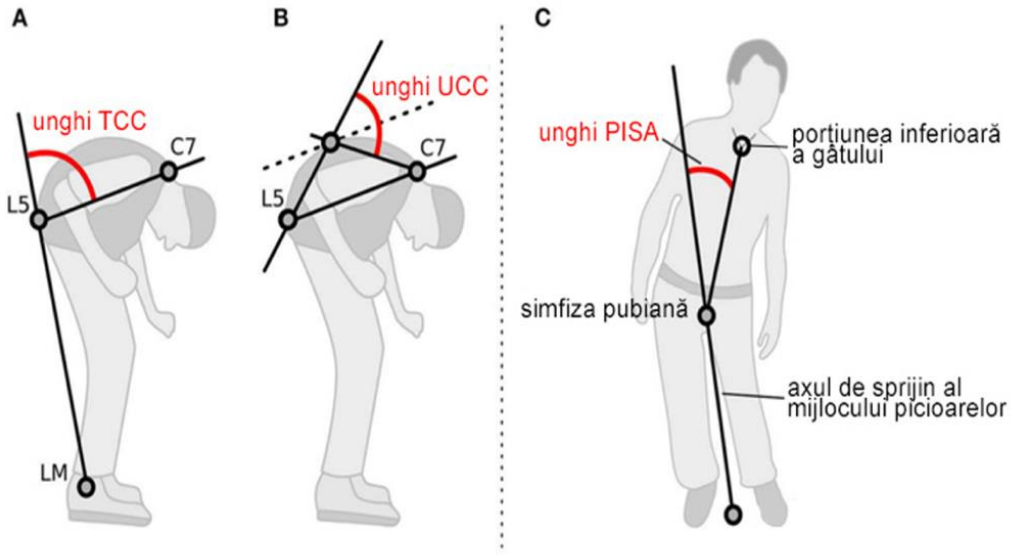


Figure 2.1. Postural angle assessment method

Methods for statistical evaluation of the results. Statistical analysis was performed using the R program for statistical analysis (version 1.0.136). To account for ordinal scaling (number of points assigned to the evaluation) of the freezing gait evaluation criteria, mixed models of cumulative linkages with a logical link function (engl., cumulative link mixed models with a logic link function) [168]. For all models, the gait freezing rating was included as a dependent variable and various other fixed and random effects as independent variables, according to the specific model:

Model 1: Patient examination at follow-up visit to investigate the immediate effect of medication, stimulation and their interaction on the severity of gait freezing in challenging situations.

- Fixed independent variables: : medication (OFF-med vs. ON-med), stimulation (OFF-stim vs. ON-stim), challenging situations of gait freezing (hesitation to initiate gait vs. hesitation to return vs. hesitation in open space vs. hesitation to reach destination).
- Independent random variables: random intercept of participants.

Model 2: patient examination at long term after stimulus initially instituted.

- Fixed independent variables: time period that elapsed after stimulus institution, challenging situations, medication
- Random independent variables: random intercept of participants.

Model 3: assessment of the beneficial effect of stimulation added to the best effect achieved by medication alone.

- Fixed independent variables: time elapsed since the stimulus was instituted, challenging situations.
- Random independent variables: random intercept of participants.

Post-hoc tests were performed with Tukey correction for multiple comparisons. The predefined level of significance was set at $p<0.05$. Inter-rater agreement statistics (weighted kappa) were used to assess agreement between two raters on the gait freezing severity scale for the total gait freezing score and each item separately.

Clinical variables (age, disease duration, UPDRS motor score, UPDRS total score and PIGD score) were compared in two groups of patients (patients with gait freezing only on 180o rotation versus patients with gait freezing in all challenging situations) using a t-test for normally distributed clinical variables and the non-parametric Wilcoxon test for non-normally distributed clinical variables. Correlations between gait freezing severity score and PIGD score, UPDRS-II

item 14, total UPDRS, UPDRS-III and age were examined using Spearman correlation coefficient. The level of statistical significance was set at $p<0.05$.

To investigate the predictability of the effect of DBS on gait freezing, (1) regression analysis and (2) receiver-operating-characteristics curve (ROC) analysis were performed.

(1) For the regression analysis, the effect of DBS on gait freezing (follow-up stim-ON minus baseline) was included as a dependent variable. To compare the predictability of the different outcomes used to measure the effect of DBS on gait freezing, a separate regression analysis was performed with the effect of DBS measured with (a) 180o return, (b) total gait freezing score and (c) UPDRS item 14 as dependent variables. An ordinal regression analysis was used to account for ordinal scaling of the dependent variables.

A stepwise backward regression approach was used to identify relevant predictors of the effect of DBS on gait freezing. After multicollinearity was checked, the following independent, predictor variables were included: the L-DOPA response of 180o turning at baseline, the L-DOPA response of UPDRS item 14 at baseline, and the L-DOPA response of UPDRS III at baseline.

McFadden Pseudo R2 was calculated to assess model fit. A Pseudo R2 of > 0.2 was considered model fit.

(2) After identifying the best predictive tool, an ROC analysis with calculation of area under the curve (AUC) was performed to investigate the predictive ability of the variables in identifying patients who took advantage of DBS by reducing freezing gait symptoms and patients who did not take advantage, remaining with the same freezing gait manifestations.

For the analysis of 180o return modes inter-rater reliability was determined by calculating the Cohen's kappa coefficient (κ). A Chi-Square test comparing the frequency of return strategies under different treatment conditions was calculated. Descriptive statistics and test for normality (Shapiro-Wilk) were performed for all variables. Differences between the three groups of patients (spin/mixed/step) were analysed with the Kruskal-Wallis test. Also, patients who changed their strategy and those who used the same strategy were compared with the Mann-Whitney test or student t-test, as appropriate.

Mann-Whitney-U tests for group comparisons were performed for statistical analysis of postural disturbance. For inter-rater and intra-rater test-retest reliability, intraclass correlation coefficients (ICC) were calculated [14]. Minimum detectable change scores were calculated for the TCC, UCC and Pisa angle for both cohorts separately according to previously established consensus [98]. Linear models were calculated for the effects of disease, age and sex. Logarithmic transformation was used when the data did not correspond to linearity or if the data were not normally distributed. Post-hoc tests were performed with Tukey correction for multiple comparisons. The significance level of the results was set for the 95.0% confidence interval.

Linear mixed models were calculated for TCC angle, UCC angle and Pisa angle included as dependent variables. Drug and stimulation were included as fixed effects, as were random intercepts for participants. To investigate whether subgroups improved differently with medication and/or stimulation, a model was set up that included the TCC and UCC angles as dependent variables, and as independent variables were the interactions medication, stimulation, random intercept for participants.

To achieve the study objective of the carry-over effect of stimulation patients were investigated from baseline OFF-medication to follow-up OFF-medication/OFF-stimulation. Fixed variables were (1) time from stimulus institution to follow-up visit; (2) random intercept for participants. To assess the additional effect of stimulation on postural disturbances, postural disturbance manifestations were compared before the intervention with medication only, then after the intervention with stimulation and with medication. TCC, UCC and Pisa angles were included as dependent variables in linear mixed models with time as fixed effect and subjects as random intercept. To investigate whether the effect of medication and stimulation differed

between male and female participants, gender was added as an additional factor to the linear mixed model used to study the previous objective, and gender-medication interactions as well as gender-stimulation interactions were considered. To identify possible predictors of the effect of stimulation, linear regression analyses were performed with either the difference from baseline OFF-medication to follow-up OFF-medication/ON-stimulation or from baseline ON-medication to follow-up ON-medication/ON-stimulation as dependent variables. After checking for multicollinearity, the following independent predictor variables were included: age, UPDRS part III L-DOPA responsiveness, and UPDRS item 28 (posture) L-DOPA responsiveness. For linear models, post-hoc tests were performed with Tukey correction for multiple comparisons.

3. Frequency and severity of gait freezing up to and after STN-DBS intervention.

3.1 Effect of STN-DBS on the phenomenon of gait freezing in patients with Parkinson's disease.

Out of the total number of 192 patients included in the study who were treated with STN-DBS 124 patients according to UPDRS point 14 had a score greater than or equal to 1, which led to their inclusion in the research group of the freezing gait phenomenon. The group of patients consisted of 82 men (66%) and 42 women (34%). Mean age (± SD) was 61.3 (± 7.6), mean duration of BP was 14.1 (± 5.5) years. Of these 124 patients, who were selected according to item 14 in the OFF-medication state at baseline, 85 patients improved in the ON-medication state, 36 did not improve and three patients had worsening of gait freezing. Of the 85 L-DOPA-sensitive patients, gait freezing was absent in the ON-medicated state in 67 patients, while 18 experienced partial improvement.

The results of the baseline video analysis in the OFF-medication state, which was performed "blind", show that of the 124 patients with UPDRS item 14> 0 in 19% of patients (n = 24) there were no episodes of gait freezing at video assessment (score = 0) and 81% (n = 100) experienced freezing in at least one challenging situation. Inter-rater agreement of two raters for frequency and severity of gait freezing based on video recording was very good for hesitation at gait initiation, turning and reaching the destination (k = 0.896, k = 0.903, k = 0. 864, respectively) and good for open space gait assessment and total gait freezing score (k = 0.775 and k = 0.747). The 180o turning maneuver is the most common circumstance causing gait freezing (73.4%) of all conditions tested in this study. The frequency of hesitation on initiating gait, hesitation on reaching a destination, and hesitation in open spaces are quite similar at baseline in the OFF-medication condition (51.6%, 50.8% and 48.4%, respectively), otherwise in all other conditions hesitation on initiating gait is the least frequent gait freezing provoking circumstance. Gait freezing caused by three manoeuvres, namely turning, initiating gait, reaching destination was present in 12 patients (12%), and freezing at other three manoeuvres: initiating gait, reaching destination and open space - only in two patients (n=2). The most common combination was gait freezing in all four challenging conditions together (43%, n=43).

Circumstances causing freezing of gait were correlated with relevant clinical parameters. The video-recording-based total gait freezing severity score showed a stronger correlation with the PIGD score ($r = 0.685$, $p < 0.01$) than with the motor score, UPDRS III ($r = 0.282$, $p < 0.01$) and total UPDRS score ($r = 0.324$, $p < 0.01$). There was no correlation with age at surgery, disease duration and age at disease onset. Compared to patients who experienced freezing of gait in all challenging situations, patients with hesitancy only on return had a significantly lower PIGD score (7.23 ± 5.13 versus 12.41 ± 3.57, $p < 0.0001$) and a lower total UPDRS score (median 70 (17) versus median 78 (32), $p < 0.05$). There was no difference in UPDRS III scores (39.5 ± 10.85 versus 48.3 ± 16.74, $p > 0.05$). Overall correlations of gait freezing during turning are more strongly related to the PIGD score, which denotes axial dysfunction, than to complex

measures of Parkinson's disease severity, consistent with the notion that gait freezing during 180o turning is the most sensitive challenging manoeuvre.

3.2 Effect of levodopa and deep brain stimulation of the subthalamic nucleus on the phenomenon of gait freezing

In accordance with Model 1 of investigation we investigated the immediate effect of medication, STN-DBS and their cumulative effect on the severity of gait freezing. According to the obtained data, positive effects in reducing the freezing phenomenon had medication ($p < 0.0001$, Chi-square = 189.0, effect size r = 1.2), stimulation ($p < 0.0001$, Chi-square = 146.5, effect size r = 1.1), and their combination: medication-stimulation ($p = 0.004$, Chi-square = 8.2, effect size r = 0.3). Furthermore, post-hoc comparisons showed that gait freezing severity was reduced in ON-stim ($p < 0.0001$) and ON-med ($p < 0.0001$) compared to the OFF-med/OFF-stim condition at follow-up (Figure 2). The effect size of the isolated stimulation effect on gait freezing severity was not statistically significant compared to the isolated medication effect ($p = 0.811$). Interestingly, however, the combination of stimulation and medication had a stronger effect on reducing gait freezing severity than either intervention alone (p for both comparisons <0.0001) (Figure 2).

The research was conducted according to Model 2 of the investigation. OFF-medication and ON-medication conditions for baseline versus follow-up were performed with the same assessment instrument.

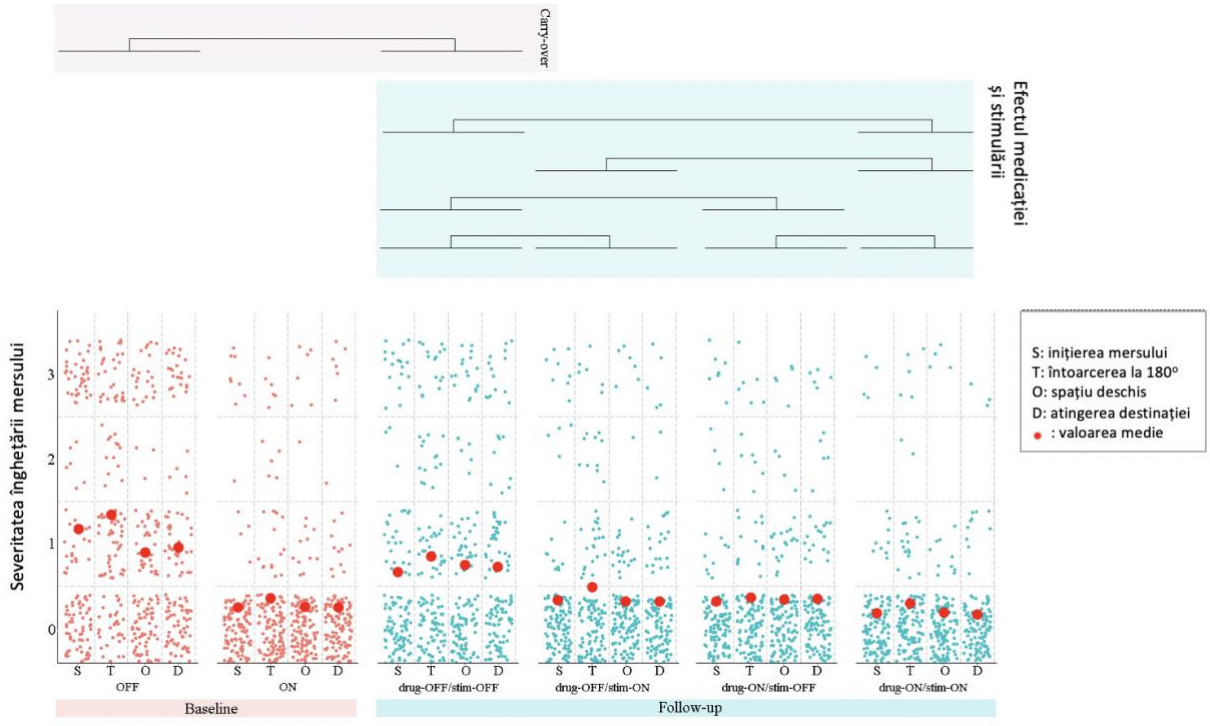


Figure 3.2. Severity of gait freezing at baseline and follow-up in four different challenging situations.

Statistically significant results of reduced gait freezing were found for the challenging situations of gait freezing ($p<0.0001$, Chi-square = 26.8, effect size r = 0.5), the length of time

after DBS ($p<0.0001$, Chi-square = 17.1, effect size r = 0.4), and their cumulative effect ($p = 0.04$, Chi-square = 8.3, effect size r = 0.3). Statistically significant were also the time-drug relationships ($p < 0.0001$, Chi-square = 31.8, effect size r = 0.5, which can be explained by the carry-over effect of the stimulation (Figure 2).

In post-hoc comparisons, hesitation to turn differed from hesitation to initiate walking ($p < 0.0004$), hesitation in open space ($p = 0.0018$) and hesitation to reach a destination ($p = 0.0046$), respectively. This again demonstrates that the turning manoeuvre is the most sensitive manoeuvre to cause gait freezing.

Different challenging situations for gait freezing episodes are differently susceptible in the long term, as hesitation during turning and at gait initiation improved significantly between baseline and the follow-up visit in the OFF-medication condition ($p <0.0001$, respectively), whereas hesitation in free space and at reaching a destination did not improve ($p = 0.7$ and $p = 0.1$, respectively).

Investigational model 3 compares the ON-med condition at baseline with the ON-med condition at follow-up. A statistically significant main effect of time period since DBS institution was observed ($p = 0.01$, Chi-square = 5.8, effect size r = 0.2), thus demonstrating that gait freezing severity was reduced at follow-up and therefore stimulation has an additional beneficial effect on gait freezing severity compared to L-DOPA testing in the ON-med condition at baseline.

In conclusion, we investigated the effects of STN-DBS and L-DOPA on gait freezing in different challenging situations in 124 BP patients with gait freezing using a scale based on video analysis of a standard gait sample. Our results show that at ten months of treatment using STN-DBS and L-DOPA there is an improvement in the appearance and severity of gait freezing; the combined intervention of medication and stimulation has a stronger impact on the severity of gait freezing; gait freezing is similarly reduced in all challenging situations and turning 180 o is the most sensitive manoeuvre for assessing gait freezing. In addition, we found a strong carry-over effect on gait freezing in the standard protocol used in the study and hypothesize that it is the stimulation that is responsible for this effect.

3.3. Identifying predictors for improving gait freezing

From a clinical point of view, a predictor is needed that can predict the improvement of the patient's condition after deep brain stimulation intervention in the worst condition. This is the time when stimulation still works but the drugs do not work optimally, e.g. during the OFF-drug phase or at night. As predictor indices, we chose the return task, total freezing gait score and UPDRS item 14.

Given these results, an ROC analysis was performed to calculate statistical power for the purpose of separating the improved (patients who improved at least 1 point from baseline OFF-med to follow-up OFF-med/ON-stim) from the non-improved (Figure 3). The AUCs were 0.857 for the return task, 0.603 for the UPDRS14 item, and 0.583 for the UPDRS III total. Thus, return burden is the best predictor and a baseline response to L-DOPA, with a cutoff of -0.5, shows the best specificity (0.80) and sensitivity (0.873) for separating people with a prospect of improvement from patients who do not.

The results of this study show that the return strategy is an easily identifiable test and is associated with the current motor status of people with BP. The return strategy certainly cannot replace the full assessment of gait function, but it can be a useful or general parameter for

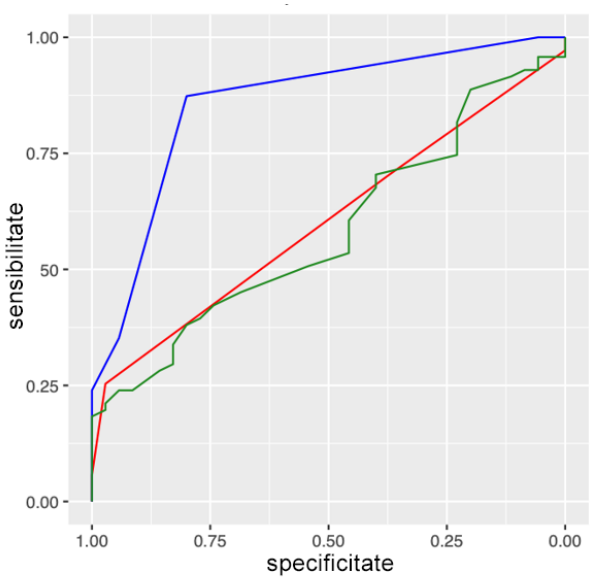


Figure 3.3. ROC curve for the analysis DBS prediction.

mobility examination. There are several questions that should be studied. For example, whether or not the fall is related to the return strategy, which could also determine specific physiotherapy training and recommendations for patients. Another interesting area would be to look for the relationship between behaviour and, in particular, risk-seeking behaviour and return strategy. This has not been done in the current cohort, but we wanted to present this finding to encourage more research in this seemingly simple and easy to test direction. The ability to predict the effect of STN-DBS on gait freezing has important significance for clinicians, patients and caregivers, as it can aid clinical decision-making and help individualize necessary treatment. One of the aims of this study was to identify the best objective clinical test that could quantify the effect of STN-DBS on gait freezing.
The results allow us to conclude that improvement in gait freezing during the 180o turning manoeuvre under the action of dopaminergic drugs before surgery (L-DOPA test) is the most effective predictor.

4. Results of postural disorder assessment: camptocormia and Pisa syndrome

4.1 Effect of levodopa and subthalamic nucleus deep brain stimulation exerted on postural alignment in patients with PD

One hundred and ninety-two patients with idiopathic PD diagnosed according to UK Brain Bank criteria were included in this study. The control group consisted of 78 healthy subjects aged 30-79 years, 10-20 people from each decade. Exclusion criteria were neurological diseases other than BP, or injuries that might have affected gait and posture.

Healthy subjects were recruited from patients' relatives. BP patients and healthy subjects did not differ in age (BP: 59.0 (8.8); SS: 55.8 (14.2); p = 0.054) or in gender distribution (F/M: BP: 62/130; SS: 32/43; p = 0.146, Chi-square = 2.1). Female and male patients with BP did not differ in disease duration, disease severity (UPDRS total, UPDRS III), anti-parkinsonian medication or clinical postural assessment (UPDRS item 28) (p> 0.05). The significant difference was only the age of men and women (p = 0.003; women = 61.8 (8.5); men = 57.7 (8.7)). To determine the reliability and to assess the importance of the postural alignment indexes, intra-class values (ICC) were determined, thus for the TCC angle the value was 0.95 (95% CI: 0.94-0.95), which is an excellent reliability, for the UCC angle - 0.83 (95% CI: 0.80-0.84), which is a good reliability, and for the Pisa angle -0.71 (95% CI: 0.67-0.74), which is a moderate reliability.

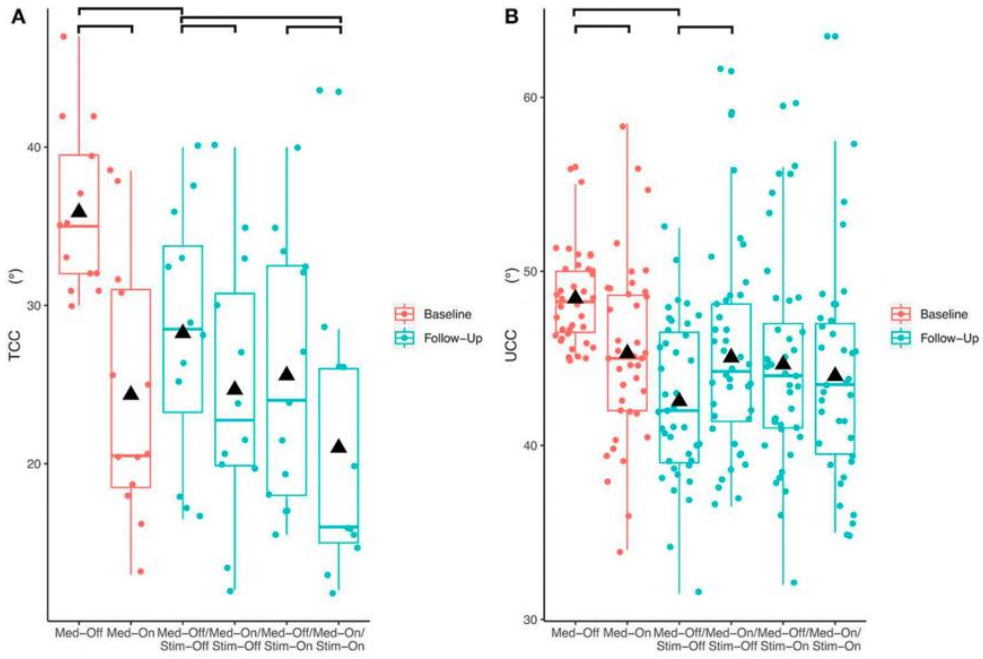


Figure 4.1. Effect of different pre- and post-surgical treatment conditions on total camptocormia (TCC) - A and upper camptocormia (UCC) - B angles.

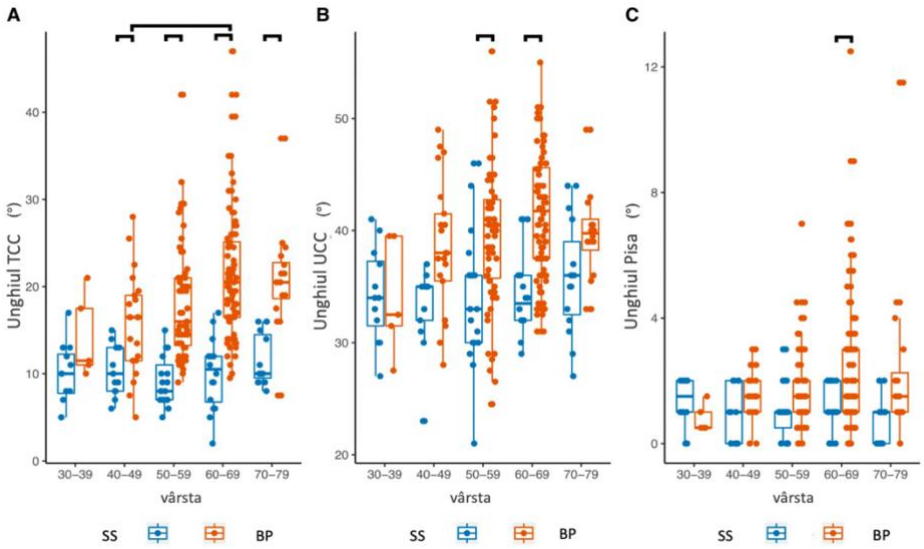
For healthy subjects, the minimum detectable change (MDC) values were 2.2° for the TCC angle, 5.1° for the UCC angle and 1.2° for the Pisa angle, respectively. For patients with BP, the MDC values were 3.7° for the TCC angle, 6.7° for the UCC angle and 2.1° for the Pisa angle respectively. Figure 4 shows the correlations between the measured angles and the clinical assessment (UPDRS item 28).

The correlation coefficients show a weak relationship between the two methods for all three angles. For the TCC angle and the Pisa angle the coefficients are slightly higher than for the UCC angle. Slope analysis of the different correlations revealed significant differences between TCC versus UCC ($p < 0.001$) and TCC versus Pisa ($p = 0.008$), but not UCC versus Pisa ($p = 0.733$).

Figure 4.2. Posture of BP patients (red) versus SS subjects (blue) in relation to different decades of age for A) TCC angle (total camptocormia), B) UCC angle (superior camptocormia) and C) Pisa angle.

4.2. Postural alignment in healthy subjects and patients with Parkinson's disease.

Within the group of healthy subjects, the effect of age was not statistically significant for the three postural alignment angles (TCC-angle: p = 0.303, F = 1.24; UCC-angle: p = 0.665, F = 0.6; Pisa-angle: p = 0.457, F = 0.92), indicating that neither TCC-, UCC- nor Pisa-angle



increased with advancing age up to 80 years. At the same time in healthy subjects a significant difference between men and women was detected, with a more pronounced bending in men on average by 1.6° for the TCC angle (p = 0.03, F = 4.9). Similar results were found for the UCC angle, with men having a more pronounced bending posture on average by 2.9° compared to women (p = 0.011, F = 6.7). No significant gender effect was found for the Pisa angle (p = 0.81, F = 0.06). No significant age interaction was found between genders (p> 0.05), indicating that the development of postural abnormalities did not worsen differently between genders in different age groups. Patients with BP show alterations in postural alignment that progress with age compared to healthy subjects. A multivariate analysis of the diagnostic and age interrelationship was performed. A significant effect of group (p < 0.001, F = 183.6), age (p = 0.001, F = 4.7) and age*group interaction (p = 0.046, F = 2.5) was found for TCC angle. Post-hoc comparison showed that for the group effect, subjects with BP had higher TCC angles than SS for the age categories 40-49 (p = 0.045), 50-59 (p < 0.0001), 60-69 (p < 0.0001) and 70-79 (p = 0.004) years.

For the effect of age, a significant difference was found in BP patients when comparing the fifth and seventh decades (40-49 and 60-69; p = 0.005) (Figure 5A). The significant age/group interaction indicates that postural alignment deterioration over time is greater in people with BP compared to SS. A significant group effect was identified for UCC angle (p <0.001,F = 57.7).

Post-hoc testing showed significant differences between people with BP and SS for decades six and seven (50-59; p = 0.003 and 60-69; p <0.001) (Figure 5B). For the Pisa angle, a

significant group effect was found (p <0.001, F = 36.0). Post-hoc tests showed a significant difference between people with BP and SS for the 60-69 age group (p = 0.026) (Figure 5C).

4.3. Results of the effects of interventions depending on the severity of the postural abnormality.

Investigation of patients with camptocormia (CCT angles ≥30◦) revealed significant isolated effects of medication (p <0.001, F = 17.9) and stimulation (p = 0.008, F = 8.0) for CCT angles (Figure 6). Patients with camptocormia were more likely to have substantial improvement, while patients with normal CCT (19%) demonstrated unchanged values. Of the 131 patients with tilted posture, 55 patients improved to a normal angle of <10.9◦ after surgery. The mean CCT of 35.9◦ in the 13 patients with camptocormia improved to 21.0◦, and two of these patients reached the limit of healthy posture. Separate analysis of patients with upper camptocormia (UCC angles ≥45◦), found no significant effect of medication or stimulation. For the two patients with Pisa syndrome, statistical analysis could not be performed because of the small group size.

Analysis of the subgroups of postural disorder patients in our study in terms of the separate action of medication and stimulation on the TCC index demonstrated a beneficial action of both medication (p < 0.0001, F = 36.4) and stimulation (p < 0.0001, F = 15.4). The same was demonstrated for the UCC angle: medication (p <0.0001, F = 13.2) and stimulation (p <0.0001, F = 11.3). Regarding the Pisa angle, only 2 participants had clinically diagnosed Pisa syndrome. Patients with Pisa-normal and Pisa-slanting angle were included in the model, revealing a statistically significant interaction for the Pisa-slanting angle subgroup (p <0.0001, F = 309.1), while the stimulation subgroup was not significant (p = 0.716, F = 0.3).

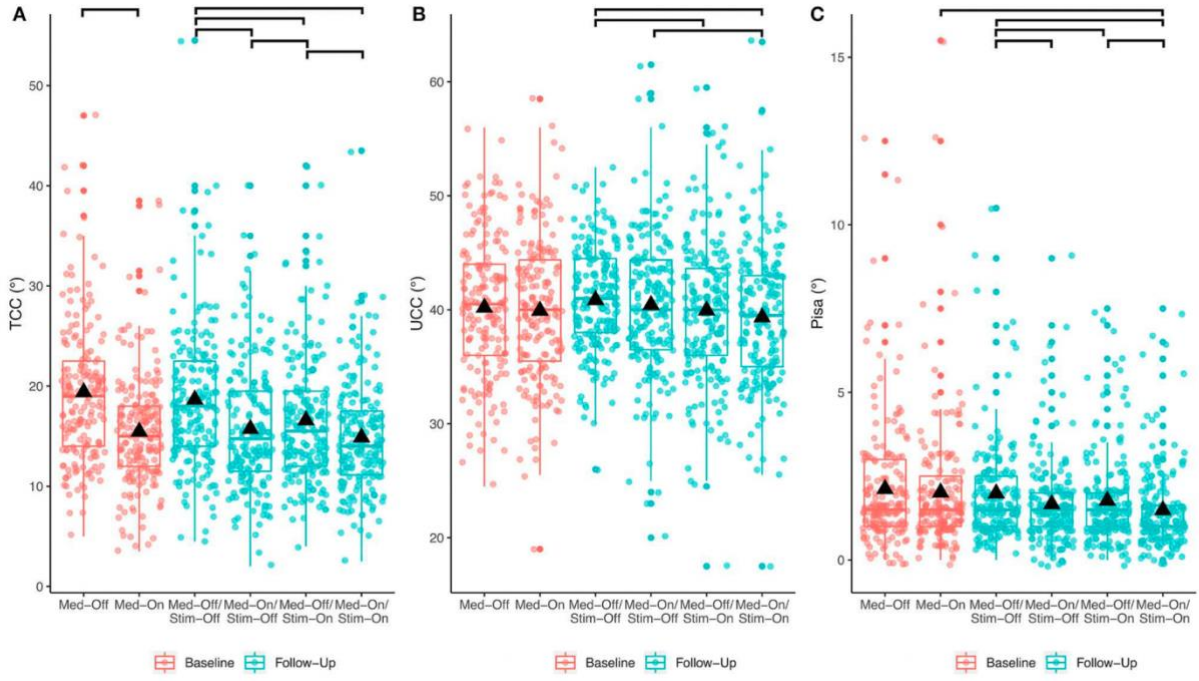


Figure 4.3. Effect of any pre- and post-surgical treatment condition for the entire cohort of BP patients.

These results denote that patients with higher values of TCC or UCC angles improved to a greater extent by both medication and stimulation compared to patients who were less affected

(Figure 7). Moreover, patients with a lateral tilt of posture had a stronger improvement by medication compared to those without lateral tilt, but the effect of stimulation was similar for the subgroups of patients with Pisa syndrome.

Carry-over effect of stimulation for TCC angle in patients with camptocormia.

Analysis of the entire patient cohort (n=192) with respect to the carry-over effect of stimulation from baseline (med-OFF) to follow-up assessment (med-OFF/ stim-OFF) identified no statistically significant time period effects for TCC ($p = 0.109$, $F = 2.6$), UCC ($p = 0.153$, $F = 2.1$) or Pisa ($p = 0.969$, $F = 0.0$) angles. However, a significant carry-over effect ($p < 0.01$, $F = 9.5$) was found when patients with camptocormia (TCC angles ≥30◦) were analyzed separately (Figure 7).

Effect of DBS on Pisa syndrome in correlation with time since onset and medication.

Regarding the comparison from baseline med-ON to follow-up med-ON/stim-ON assessment, a statistically significant time effect was found for Pisa angle ($p <0.0001$, $F = 21.6$), but not for TCC ($p = 0.125$, $F = 2.4$) or UCC ($p = 0.176$, $F = 1.8$) angles when the analysis included all participants.

Benefit of stimulation in relation to sex of postural disorder patients.

No significant gender-stimulation interaction was established for TCC angle ($p = 0.449$ $F = 0.6$), meaning that male and female patients benefit similarly from DBS. Although a significant interaction was found for gender - medication ($p = 0.047$, $F = 3.1$), the post-hoc comparison showed no significant differences between males and females when comparing changes from med-OFF to med-ON. For UCC and Pisa angles, there were no significant gender-medication or gender-stimulus interactions.

Identifying predictors of the effect of stimulation.

We included age and L-DOPA responsiveness of UPDRS III and UPDRS 28 item at as independent variables in a linear regression model with the effect of DBS on TCC, UCC and Pisa syndrome angles as dependent variables. For TCC, the model showed significant values ($p = 0.006$), but with low predictability ($R2 = 0.05$). The models for UCC and Pisa syndrome angles had no statistical significance, with p-values equal to 0.09 in both cases.

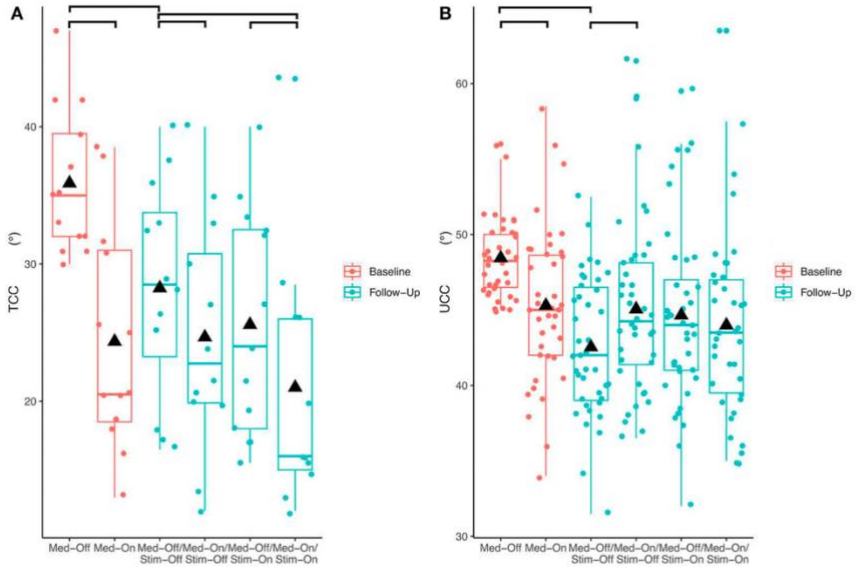


Figure 4.4. Effect of different pre- and post-surgical treatment conditions on total camptocormia (TCC) - A and upper camptocormia (UCC) - B angles.

5. Discussion on the effect of STN-DBS on gait and posture disorders in patients with Parkinson's disease

This study investigated the effect of subthalamic nucleus deep brain stimulation and L-DOPA medication on gait freezing and postural disorders in patients with BP. Gait freezing is a disabling and unpredictable symptom of dopaminergic treatment. Although STN-DBS is a well-established therapy for motor symptoms of BP, its efficacy in treating gait freezing is inconsistent, with conflicting reports. In this study, combined intervention with medication and stimulation was found to have a stronger impact on gait freezing, and 180-degree turning was found to be the most sensitive manoeuvre for its assessment. A strong carry-over effect on gait freezing was also observed in the standard protocol used in the study, and it is hypothesised that stimulation is responsible for this effect. Predicting the effect of deep brain stimulation on gait freezing in BP is important for clinical decisions and treatment individualization. Identifying the best clinical test to quantify the effect of STN-DBS on gait freezing is one of the aims of the study, and the improvement of gait freezing during the 180o turning manoeuvre under the action of dopaminergic drugs before surgery (L-DOPA test) is the most effective predictor. Turning strategy in BP patients has been little studied so far but is an important sign of their motor status. In this study, it was found that return strategy changes with motor status and that patients who choose the spin return strategy have a better motor score than those who choose the step return strategy. However, spin turning can be riskier and can lead to falls. Camptocormia is a common postural deformity in Parkinson's disease patients that can affect their ability to move around and perform everyday activities. There are few effective treatments for this condition, but deep brain stimulation has become an increasingly popular therapeutic option. Recent studies have shown that STN-DBS can have a significant therapeutic effect on camptocormia and can bring about great improvements especially in patients complicated with this postural deformity. This study examined the reliability of a free web-based application, called NeuroPostureApp ©, for assessing postural alignment and compared posture between healthy individuals and those with BP. The study found that the app has good to excellent reliability in assessing total and superior captocormial angles (TCC and UCC), but only moderate reliability in assessing tilt angle in Pisa syndrome. Study results suggest that the NeuroPostureApp © is more sensitive to postural differences than the traditionally used UPDRS 28 item for posture assessment. In addition, posture assessment with this app does not require any other technical equipment, as photographs can be easily analysed to measure postural angles. The study calculated the minimum detectable change values for each of the three angles, which can be useful in interpreting the effects of the applied treatment. The study also developed its own normative data for the postural alignment of healthy controls in the anteroposterior (AP) and mediolateral (ML) directions for different age groups and investigated the effect of gender. The results showed that males had a more tilted posture than females for the TCC and UCC angles, and the effects were strongest for the UCC angle. This may indicate differences in postural control and/or biomechanics between genders. Overall, the study suggests that the NeuroPostureApp © is a useful tool for assessing postural alignment in BP and can be used effectively to monitor patient progress during treatment. Also, normative postural alignment data for healthy controls may be useful to compare patients with BP to normal values and to assess treatment efficacy. Treatment had minor effects on postural angles in patients with normal posture. Patients with abnormal posture had significant but small improvements, and patients with camptocormia had the greatest improvements. Combination treatment had a slightly greater effect than isolated stimulation for the TCC angle.

GENERAL CONCLUSIONS

1. Freezing of gait is a common episodic gait disorder in patients with Parkinson's disease, and the underlying pathophysiological mechanism is not fully elucidated, involving deficits in the

connectivity of cognitive, motor and affective brain networks, and is a highly variable and difficult symptom to provoke under clinical conditions. Of all four challenging conditions triggering the freezing gait phenomenon tested in this study, the 180o turning manoeuvre was found to be the most sensitive method of provoking freezing gait (73%) in patients with Parkinson's disease.
2. The results of the study found that the improvement in the severity of the freezing gait phenomenon during the 180o turning manoeuvre under the action of pre-operative dopaminergic drugs (L-DOPA test) is the most effective predictor for the efficacy of deep brain stimulation intervention. Thus, if the severity of the gait freezing phenomenon improves during the pre-operative L-DOPA test by 1, 2 or 3 points respectively, the probability of ≥ 1 point improvement by post-operative subthalamic nucleus deep brain stimulation intervention is 79%, 80% or 100%.
3. General strategies of return modalities have not yet been addressed in detail in patients with Parkinson's disease. Of the three return modalities analyzed in this study (step, spin, mixed), we found that the choice of the "spin" type indicates lower motor severity, which proves that the return strategy in patients with Parkinson's disease correlates with disease severity and is useful for estimating motor impairment. Possibly this clinical phenomenon is also based on pathophysiological phenomena such as impulsivity and the patient's affective state.
4. Treatment by surgical deep brain stimulation of the subthalamic nucleus in patients with Parkinson's disease offers an improvement in the appearance and severity of the freezing gait phenomenon and the combined intervention of stimulation with dopaminergic medication has a stronger impact on the severity of freezing gait.
5. According to the results of the study, postural deviation in patients with Parkinson's disease progresses with age, which is also confirmed by other researchers. The total camptocormia angle value $\geq 30°$ is a reliable diagnostic criterion for total camptocormia, empirically demonstrated by us and supported by the results of other research, whereas the upper camptocormia angle and Pisa angle values require combined examinations with detailed clinical information. At the same time, the study conducted allowed us to find that the NeuroPostureApp used in this paper for the quantitative assessment of postural alignments proved to be a reliable tool in the identification of postural disorders.
6. Both dopaminergic medication and subthalamic nucleus deep brain stimulation intervention improved postural alignment deviated in the antero-posterior and medio-lateral direction in patients with Parkinson's disease. Treatment effects were strongest for patients with severe postural deficiencies, with a large proportion of patients regaining their physiological posture. Treatment effects were strongest in patients with camptocormia.

PRACTICAL RECOMMENDATIONS

1. It is recommended that the 180-degree turn test be used in clinical practice to evoke and assess gait freezing in patients with Parkinson's disease.
2. It is recommended to use the change in the gait freezing score at 180 degree turn as a method of predicting the subsequent effect of subthalamic nucleus deep brain stimulation on gait freezing.
3. The use of the spin turn strategy is recommended for the assessment of the severity of motor impairment in patients with Parkinson's disease.
4. The method of treatment by deep brain stimulation of the subthalamic nucleus is recommended for patients with Parkinson's disease and gait freezing phenomenon, as well as for those with pathological postural deviations, especially of the total camptocormia type.

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LIST OF PUBLICATIONS

and scientific events where research results have been presented to the doctoral thesis in medical sciences with the topic "Effect of deep brain stimulation on gait and posture disorders in patients with Parkinson's disease", carried out within the Scientific Laboratory of Functional Neurology of the Institute of Neurology and Neurosurgery of Mrs. Gavriliuc Olga, State University of Medicine and Pharmacy "Nicolae Testemitanu"

- Articles in ISI journals, SCOPUS and other international databases:

1. **Gavriliuc O**., Paschen S., Andrusca A., Schlenstedt C., Deuschl G. Prediction of the effect of deep brain stimulation on gait freezing of Parkinson's disease. *Parkinsonism & Related Disorders*. 2021; 87:82-86. ISSN: 1353-8020. Disponibil online la: https://doi.org/10.1016/j.parkreldis.2021.04.006 (**Scopus**, **IF$_{ISI}$: 3,9)**
2. **Gavriliuc O**., Paschen S., Andrusca A., Helmers AK., Schlenstedt C., Deuschl G. Clinical patterns of gait freezing and their response to interventions: an observer blinded study. *Parkinsonism & Related Disorders*. 2020; 80:175–180. ISSN: 1353-8020. Disponibil online la: https://doi.org/10.1016/j.parkreldis.2020.09.043 (**Scopus**, **IF$_{ISI}$: 4,3)**
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SUMMARY

Gavriliuc Olga, **"Effect of deep brain stimulation on gait and posture disorders in patients with Parkinson's disease"**, PhD thesis in medical sciences, Chisinau, 2023

Thesis structure: introduction, four chapters, general conclusions and practical recommendations. The work consists of 100 pages of basic text and includes 6 tables and 13 figures, and the bibliography in the work includes 194 sources.
Keywords: Parkinson's disease, STN-DBS, L-DOPA, gait freezing, postural disorders, camptocormia, Pisa syndrome.
Thesis field of study: neurology.
Aim: to evaluate the effect of subthalamic nucleus deep brain stimulation on gait freezing, camptocormia and Pisa syndrome in patients with Parkinson's disease in order to develop an algorithm to select eligible candidates for this intervention.
Research objectives: to assess the frequency and severity of gait freezing in patients with Parkinson's disease and to identify the most sensitive circumstances for provoking gait freezing phenomenon during a standardized gait task; to identify an objective clinical test with the highest predictive value for estimating the improvement of gait freezing in patients with Parkinson's disease following subthalamic nucleus deep brain stimulation intervention; to analyze the types of turning strategies in patients with Parkinson's disease and correlate them with the severity of motor impairment; determining the effectiveness of subthalamic nucleus deep brain stimulation intervention for the treatment of gait freezing in patients with Parkinson's disease; characterising postural alignment in patients with Parkinson's disease, namely anterior tilt differentiated into total and superior camptocormia and lateral tilt, referred to as the 'Pisa angle' using a standardised digital instrument (NeuroPostureApp); investigating the effect of subthalamic nucleus deep brain stimulation on postural alignment in patients with Parkinson's disease.
Scientific novelty and originality: the results of this study showed that ten months after STN-DBS surgery there is an improvement in the appearance and severity of gait freezing; the combined L-DOPA and STN-DBS intervention has a stronger impact on the severity of gait freezing; gait freezing is similarly reduced in all challenging situations; 180o turning is the most sensitive manoeuvre for assessing gait freezing; improvement of gait freezing during 180o turning manoeuvre during gait under the action of pre-operative dopaminergic drugs is the most effective predictor; we identified good to excellent reliability in assessing TCC angle and UCC angle with the NeuroPostureApp © created and implemented at the Department of Neurology in Kiel in 2018; prevalence of camptocormia is 6.8% and Pisa syndrome at 1% in patients in our cohort; both treatments, L-DOPA and STN-DBS, improved postural alignment angle in BP patients, however the effect was small for the whole cohort; patients with total camptocormia (TCC) show the greatest benefit to treatment; we found a carry-over effect in the standard protocol used in the study and our hypothesis is that it is the stimulation that is responsible for this effect.

ADNOTARE

Gavriliuc Olga, "**Efectul stimulării cerebrale profunde asupra tulburărilor de mers și postură la pacienții cu boală Parkinson**", teză de doctor în științe medicale, Chișinău, 2023
Structura tezei: introducere, patru capitole, concluzii generale și recomandări practice. Lucrarea este compusă din 100 de pagini text de bază și include 6 tabele și 13 figuri, iar bibliografia din lucrare include 194 surse.
Cuvinte-cheie: boala Parkinson, STN-DBS, L-DOPA, înghețarea mersului, tulburări de postură, camptocormie, sindrom Pisa.
Domeniul de studiu al tezei: neurologie.
Scopul: evaluarea efectului stimulării cerebrale profunde al nucleului subtalamic asupra fenomenului de înghețarea a mersului, camptocormie și sindrom Pisa la pacienții cu boală Parkinson pentru elaborarea unui algoritm de selecție a candidaților eligibili pentru această intervenție.
Obiectivele cercetării: evaluarea frecvenței și severității înghețării mersului la pacienții cu boala Parkinson și identificarea celor mai sensibile circumstanțe de provocare a fenomenului de înghețare a mersului în timpul unei sarcini de mers standardizat; identificarea unui test clinic obiectiv cu cea mai mare valoare predictivă pentru estimarea ameliorării înghețării mersului la pacienții cu boala Parkinson în urma intervenției de stimulare cerebrală profundă a nucleului subtalamic; analiza tipurilor de strategii de întoarcere la pacienții cu boala Parkinson și corelarea lor cu severitatea afectării motorii; determinarea eficacității intervenției de stimulare cerebrală profundă a nucleului subtalamic pentru tratamentul înghețării mersului la pacienții cu boală Parkinson; caracterizarea aliniamente posturale la pacienții cu boala Parkinson, și anume înclinarea anterioară diferențiată în camptocormie totală și camptocormie superioară, precum și înclinarea laterală, denumită „unghiul Pisa" prin intermediul unui instrument standardizat pe suport digital (NeuroPostureApp); investigarea efectului stimulării cerebrale profunde a nucleului subtalamic asupra alinierii posturale la pacienții cu boala Parkinson.
Noutatea și originalitatea științifică: rezultatele acestui studiu au arătat că la zece luni după operația de *STN-DBS* are loc o ameliorare în aspectul apariției și severității înghețării mersului; intervenția combinată *L-DOPA* și *STN-DBS* are un impact mai puternic asupra severității înghețării mersului; înghețarea mersului se reduce într-un mod similar în toate situațiile provocatoare; întoarcerea la 180 ^{o} este cea mai sensibilă manevră pentru evaluarea înghețării mersului; ameliorarea înghețării mersului în timpul manevrei de întoarcere la 180^{o} în timpul mersului, sub acțiunea medicamentelor dopaminergice pre-operator este cel mai eficient predictor; am identificat o fiabilitate de la bun la excelent în ceea ce privește evaluarea unghiului TCC și a unghiului UCC cu NeuroPostureApp © creată și implementată în cadrul Departamentului de Neurologie din Kiel în anul 2018; prevalența camptocormiei este de 6,8% iar sindromul Pisa la 1% la pacienții din cohorta noastră; ambele tratamente, *L-DOPA* și *STN-DBS*, au ameliorat unghiul de aliniere posturală la pacienții cu BP, totuși efectul a fost mic pentru întreaga cohortă; pacienții cu camptocormie totală (TCC) prezintă cel mai mare beneficiu la tratament; am descoperit un efect *"carry-over"* în protocolul standard utilizat în studiu și ipoteza noastră fiind că anume stimularea este responsabilă de acest efec

АННОТАЦИЯ

Гаврилюк Ольга, "**Влияние глубокой стимуляции мозга на нарушения походки и осанки у пациентов с болезнью Паркинсона",** кандидатская диссертация по медицинским наукам, Кишинев, 2023 г.

Структура диссертации: введение, четыре главы, общие выводы и практические рекомендации. Работа состоит из 100 страниц основного текста, включает 6 таблиц и 13 рисунков, библиография в работе включает 194 источника.
Ключевые слова: болезнь Паркинсона, STN-DBS, L-DOPA, замирание походки, постуральные нарушения, камптокормия, синдром Пиза.
Область исследования диссертации: неврология.
Цель: оценить влияние глубокой стимуляции субталамического ядра головного мозга на замирание походки, камптокормию и синдром Пиза у пациентов с болезнью Паркинсона для разработки алгоритма отбора подходящих кандидатов для данного вмешательства.
Цели исследования: Оценить частоту и тяжесть замирания походки у пациентов с болезнью Паркинсона и определить наиболее чувствительные обстоятельства для провоцирования феномена замирания походки во время стандартизированного задания на походку; определить объективный клинический тест с наибольшей прогностической ценностью для оценки улучшения замирания походки у пациентов с болезнью Паркинсона после вмешательства глубокой стимуляции субталамического ядра мозга; проанализировать типы стратегий поворота у пациентов с болезнью Паркинсона и соотнести их с тяжестью двигательных нарушений; определение эффективности глубокой стимуляции субталамического ядра мозга для лечения замирания походки у пациентов с болезнью Паркинсона; характеристика постурального выравнивания у пациентов с болезнью Паркинсона, т.е. переднего наклона, дифференцированного на полную и верхнюю камптокормию, и бокового наклона, называемого "углом Пиза", с помощью стандартизированного цифрового инструмента (NeuroPostureApp); исследование влияния глубокой стимуляции субталамического ядра мозга на постуральное выравнивание у пациентов с болезнью Паркинсона.
Научная новизна и оригинальность: Результаты данного исследования показали, что через десять месяцев после операции STN-DBS наблюдается улучшение появления и выраженности замирания походки; комбинированное вмешательство L-DOPA и STN-DBS сильнее влияет на выраженность замирания походки; замирание походки одинаково уменьшается во всех сложных ситуациях; поворот на 180о является наиболее чувствительным маневром для оценки замирания походки; улучшение замирания походки при маневре поворота на 180о во время ходьбы под действием предоперационных дофаминергических препаратов является наиболее эффективным предиктором; мы выявили хорошую или отличную надежность при оценке угла TCC и угла UCC с помощью NeuroPostureApp ©, созданного и внедренного на кафедре неврологии в Киле в

2018 году; распространенность камптокормии составляет 6,8%, а синдрома Пиза - 1% среди пациентов нашей когорты; оба метода лечения, L-DOPA и STN-DBS, улучшили угол постурального выравнивания у пациентов с БП, однако эффект был небольшим для всей когорты; пациенты с полной камптокормией (TCC) показывают наибольшую пользу от лечения; мы обнаружили эффект переноса в стандартном протоколе, используемом в исследовании, и наша гипотеза заключается в том, что именно стимуляция отвечает за этот эффект.