Clinical investigations of treatments for advanced Parkinson's disease

Doctoral (PhD) thesis

dr. Juhász Annamária

Doctoral School of Clinical Neuroscience (D221)

Leader of the Doctoral School: Prof. Sámuel Komoly

Leader of Research Program: Prof. József Janszky (B-5/2014)

Tutor: Prof. Norbert Kovács, Dr. Balás István

University of Pécs

Medical School

2022

1. Introduction

1.1 Parkinson's disease

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease and it has the fastest growing prevalence of all neurological diseases. Although the disease occurs generally after the age of 60, the number of young onset cases affacting working age population is increasing. The ethiology of the disaese is still unknown, apart from genetic predisposition, a role for environmental factors are also suspected.

The symptoms of PD are diverse, with dopamine being involved not only in motor control but also in mood regulation, motivation, reward and addiction, among others. Therefore many non-motor symptoms are also part of the disease. Levodopa has been used for over 50 years to treat Parkinson's disease, yet it is still the most effective symptomatic therapy. Levodopa is a precursor of dopamine production, which allows nerve cells to produce dopamine more efficiently. It can be used in both early and late stages of the disease.

1.2. Advanced Parkinson's disease

When levodopa is administered orally a large fluctuation in blood concentration is observed, leading to development of motor and non-motor complications in the long term. The phase of levodopa-induced complications is called advanced PD. In the background there is reorganization at cellular level; receptors, synaptic connections, connectivity of brain areas change. These processes are related partly to fluctuating dopaminergic stimulation and partly to ongoing neurodegeneration. In addition, as the disease progresses, autonomic nervous system involvement resulting unpredictable gastric emptying also play an important role.

Once the disease reaches a certain stage, significant fluctuations in serum levodopa level and motor fluctuations cannot be eliminated depite the best optimal per os drug therapy. In such cases, deep brain stimulation, levodopa/carbidopa intra-gestational gel (LCIG) treatment and the use of apomorphine pen and pump may be helpful. The main therapeutic goals of these treatments are to reduce levodopa-induced dyskinesia (the symptom that most negatively affects quality of life) and to reduce the length of off periods.

The usual method to characterise the presence and severity of motor symptoms is the neurological physical examination, which is recorded in a textual form. Because of individual

variations, neurological status in text form is not suitable for standardised data processing. Therefore, the use of clinical scoring scales has become of great importance in clinical trials. By using validated scales, the severity of objective symptoms is converted into scores, so that results can be objectively compared between different examiners and centres.

2. Objectives

Levodopa-induced dyskinesia is one of the most disturbing symptoms in advanced PD, and few tools have been available for its assessment. The Movement Disorders Society has highlighted the weaknesses of the Unified Parkinson's Disease Rating Scale (UPDRS) and since 2008 has recommended the use of the improved, clinimetrically validated MDS-UPDRS scale and the Unified Dyskinesia Rating Scale (UDysRS) to assess dyskinesia. The following objectives were formulated for the clinical investigation of treatment options for advanced PD using the two scales mentioned above:

1. Assessing the effectiveness of levodopa/carbidopa intestinal gel therapy (LCIG) treatment for dyskinesia

LCIG treatment is generally accepted to improve motor fluctuations by increasing the duration of on periods without dyskinesia and decreasing the duration of off periods. All longitudinal studies show dramatic improvements in health-related quality of life, but outcomes related to activities of daily living are variable. The discrepancies can be explained partially by methodology; until the publication of our article, international studies have used only the UPDRS-2, Hauser Patient Diary and UPDRS-4 scales to assess changes in lifestyle and dyskinesia.

2. Examining the effectiveness of subthalamic DBS treatment on dyskinesia

Previously, several studies have investigated the positive effects of DBS treatment in PD on motor, non-motor symptoms and quality of life (HRQoL). There are less data available on dyskinesia. It has been hypothesised, that in subthalamic nucleus deep brain stimulation, the effect in reducing active dyskinesia is smaller than in globus pallidus internus DBS treatment. However the significantly reduced per os drug dose (LED) alone will result in further improvement. Meta-analyses have shown that there is no significant difference in the efficacy

of two targets in the treatment of dyskinesia, but large international studies have used UPDRS scale data to date (2017).

Surgical planning and execution play a key role in the effectiveness of DBS treatment, and in the third part of my thesis I summarise our research relevant to surgical planning:

3. Comparison of subthalamic nucleus target coordinates with 1 and 3 Tesla MRI scans in planning deep brain stimulation surgery

Targeting errors can occur during DBS surgery, these can be caused by several factors. For example, geometric distortion in the magnetic field created during the MRI scan for surgical planning can lead to further distortion of the image information. The aim of our paper was to compare the stereotaxic target coordinates of the target areas in MRI scans acquired at different magnetic field strengths (1 and 3T) in the same patient for planning deep brain stimulation surgery with our direct morphological target assignment and the stereotaxic target coordinates automatically provided by the planning software.

The results of each clinical study are summarized in a separate chapter, as the patient population studied and the methods used are different.

4. Effects of levodopa/carbidopa intra-oral gel treatment on dyskinesia

4.1 Introduction - the levodopa/carbidopa intestinal gel (LCIG) treatment

LCIG treatment has been an accepted treatment in the European Union since 2004 and is indicated for motor complications (troublesome dyskinesia, unpredictable OFF and consequent reduction in quality of life). In Hungary, LCIG treatment has been available with social security support since 2011. While older age, vascular encephalopathy, cerebral atrophy and minor cognitive impairment are contraindications for DBS therapy, LCIG treatment can still be performed in these cases.

The treatment involves continuous and steady delivery of gel-form levodopa (levodopa/carbidopa gel) to the site of absorption in the small intestine via a PEG using a controllable pump, thus bypassing the problem of unpredictable gastric emptying. By keeping the blood concentration of levodopa nearly constant, unpredictable ON-OFF fluctuations are

improved, and in rare cases even eliminated. In addition, the severity of dyskinesia, the incidence and severity of freezing and OFF dystonia may be significantly improved.

4.2 The Hungarian Duodopa Register

The Hungarian Duodopa Register (LCIG01) was founded at the University of Pécs, independent of commercial aims and influence. By now, all Hungarian movement disorder centres (SOTE, SZOTE, Miskolc Hospital) providing LCIG treatment have joined its operation, thus creating a multicentre registry (OGYI/47439-6/2013) with clinical and research purposes, whose main objective is to evaluate the efficacy and safety of LCIG treatment in Hungarian patients. Using data from the Hungarian Duodopa Registry, we analysed whether LCIG treatment improves vital signs and dyskinesia in advanced PD after one year of treatment.

4.3 Methods

Patients:

We included 34 patients receiving LCIG treatment from the Hungarian Duodopa Registry in our prospective, open, multicentre study. 19 men and 15 women were included in the study, mean age was 67±6 years, disease duration was 12±5 years. 19 patients belonged to the rigid-akinetic form group, 15 had mixed Parkinson's disease. All patients met the UK Brain Bank criteria for Parkinson's disease. Following the recommendation for the treatment of advanced PD, the indication for LCIG treatment was severe motor fluctuations under optimal per os drug therapy.

Scales used:

Patients were examined two times, immediately before starting treatment and at 12 months. Overall severity of PD symptoms was assessed by using the Hungarian validated version of the MDS- UPDRS. The severity of dyskinesia and its impact on quality of life was evaluated by the Unified Dyskinesia Rating Scale (UDysRS), validated in Hungarian. We also used the Hauser patient diary to measure average ON time and duration of dyskinesia. The Patient's Global Impression- Severity scale (PGI-S) provided a subjective picture of the overall severity of the disease from the patient's side. To calculate the degree of non-motor (sleep-related, cardiovascular, cognitive, mood, gastrointestinal, vegetative) symptoms, we used the Non-Motor Symptoms Scale (NMSS). To further assess sleep disturbance, the Parkinson's Disease Sleep Scale version 2 (PDSS-2) specific to Parkinson's disease was used. Daytime sleepiness was measured by using the Epworth Sleepiness Scale. Neuropsychological tests were

used to assess depression (Montgomery Depression Scale) and cognitive performance (MoCA, MMSE). Health-related quality of life was quantified by using the PDQ-39 and EQ-5D scales validated in Hungarian.

Statistics

Since proof of statistical significance is not sufficient to demonstrate clinical significance, we considered the Minimal Clinically Important Difference (MCID) to be the smallest change that the patient and clinician already perceive and consider to be practically relevant when evaluating response to therapy.

Statistical analysis was performed using the IBM SPSS software package version 23.0.1 (IBM Inc., Armonk, NY, USA). As the data did not follow a normal distribution, we used a non-parametric Friedman test to determine statistical differences and the Wilcoxon sign test to compare baseline and 12th month data. For categorical variables, we used Chi2 test. The level of statistical significance was set at 0.05. McNemar's test was used to test for dichotomous variables (e.g., absence or presence of sleep problems). The magnitude of the change that occurred was characterized by the effect size indicator.

4.4 Results

At follow-up after one year, the mean levodopa dose was 1222.4±667.0 mg/day, with 3 cases receiving 24-h LCIG treatment and 31 cases receiving 16-h day treatment. 7 cases required supplementary treatment (3 with water soluble levodopa, 5 with 100-200 mg levodopa/carbidopa/ entacapone at bedtime, 2 with 4-6 mg ropinirole, 1 with 1.05 mg pramipexole, 1 with 4 mg rotigotine)

For the MDS-UPDRS Part I, non-motor symptoms of daily living, the total score decreased from 20 (median, IQR:14-23) to 16 (median, IQR:12-20, p=0.044). For motor symptoms of daily living, the score improved from 24 (median, IQR:20-29) to 18 (median, IQR:13-25, p=0.025). The change that occurred exceeded the MCID scores, and the improvement we have shown is not only statistically but also clinically significant. Fewer patients reported severe symptoms during follow-up (11 vs. 20, p=0.049, McNemar test) with the PGI-S sub-test. The PDQ-39 scale score improved from 35.4 (median, IQR:26.9-50.3) to 27.0 (median, IQR:21.3-31.4, p=0.003) (effect-size=0.52). The UDysRS total score decreased from 47 (median, IQR:36-54) to 34 (median, IQR:21-45, p=0.003), although this change was

only trend with a medium effect size (0.47), both on and off dyskinesia scores on the UDysRS 1&2) significantly improved with a large effect size (0.67-0.69).

With LCIG treatment, there were significant improvements in non-motor symptoms in the NMSS total score (p=0.027, effect-size: 0.56) and in the cardiovascular and mood sections (effect-sizes: 0.56-0.60). Sleep quality at night (PDSS-2) was significantly improved (IQR: 14-29) points (P=0.042, effect-size=0.34) , while scores of depression (based on MRDS) and daytime sleepiness (Epworth Scale) only tended to increase, the latter changes also exceeding the MCID, suggesting that LCIG treatment can enhance sleep quality to a clinically significant extent.

The adverse event profile was similar to international studies. We predominantly encountered implantation or stoma-related complications, especially in the first two weeks after implantation. No patient withdrew from the study, no treatment had to be discontinued due to adverse events.

4.5 Discussion

Our results show that 1 year of LCIG treatment significantly improves motor and non-motor symptoms of advanced PD, in addition to improving health-related quality of life. No significant difference was observed in the motor symptoms part of the MDS-UPDRS, which can be explained by the fact that the test was always performed in the on phase. Although the objective severity of dyskinesia did not significantly improve (UDysRS-3, p-value of 0.063, effect-size of 0.47), we suspect inadequate statistical power in the background.

With LCIG treatment, we observed improvements not only in motor but also in some non-motor symptoms, which may be surprising as these symptoms are thought to be partially independent from dopamine. We can conclude that shorter off periods are beneficial for non-motor fluctuations and that motor symptoms have a significant influence on mood. In addition, reducing the peak dose of levodopa has been shown in some studies to have a beneficial effect on, for example, orthostatic hypotension. Improvements in sleep quality have been suggested not only by decreasing scores on the PDSS-2 scale, but also by an increase in the duration of sleep at night detectable in the patient diary. In addition to the symptomatic improvement, quality of life also increased to a significant degree, which is congruent with the upgraded quality of life. The degree of raise in quality of life and the incidence of adverse events are comparable to those reported in international studies.

4.6 Conclusions

Our results support that LCIG treatment is effective in improving quality of life in advanced PD in both motor and non-motor symptoms, these changes are objectively reflected by the UDysRS and MDS-UPDRS scales and we recommend their use in further clinical trials.

5. The effectiveness of bilateral subthalamic deep brain stimulation for the treatment of dyskinesia

5.1 Introduction

Deep brain stimulation (DBS) treatment has been used worldwide for nearly 30 years, with over 140,000 patients having benefited globally, and there is a plenty of data on its effectiveness in terms of both motor symptoms and quality of life. The safety and efficacy of the treatment explains why the number of surgeries has been steadily increasing and the range of indications has been steadily expanding.

Using subthalamic nucleus (STN) DBS in PD, the on period without troublesome dyskinesia can be significantly lengthened (up to 6 hours) in a substantial proportion of cases. Its efficacy is not only due to the direct effect of stimulation on brain tissue, in the vast majority of cases the required daily amount of medication can be reduced, even by half of the LED. The latter phenomenon is one of the foundations of long-term cost-effectiveness.

Deep brain stimulation has been available at the Department of Neurosurgery of the University of Pécs since 2001, it is provided by social security for the symptomatic treatment of Parkinson's disease, primary dystonia, tremor, obsessive-compulsive disorder and focal epilepsy not suitable for resective surgery.

Surgical effectiveness

Since DBS treatment is expected to improve symptoms that respond to levodopa treatment, late advanced symptoms such as speech disturbance, drooling, postural instability, frequent falls, do not improve with deep brain stimulation treatment in most cases. The only exception to this rule is tremor, which can respond extremely well to stimulation even in drug-resistant patients.

A realistic outcome to expect from stimulation for patients is the achievement of an optimal state comparable to periods of on without dyskinesia with per os medication. Overall, the on period is extended by an average of 5-6 hours per day, while the on state with hyperkinesis is reduced by almost half. The duration of the off state is also reduced by almost 60%. Quality of life improves by an average of 25% as measured by the Parkinson's Disease Questionnaire (PDQ-39) scale.

5.2 Objective

Since 2004, patient care has been provided according to an integrated protocol with the Department of Neurology at the PTE: patient screening, intraoperative electrophysiological monitoring, stimulator testing and programming, medication modification and overall patient care are carried out by the staff of the Department of Neurology. Clinical research is ongoing. Our current study aims to investigate the effect of bilateral subthalamic DBS treatment on dyskinesia using the Unified Dyskinesia Scoring Scale (UDysRS).

5.3 Methods

Patients

In the present prospective study, we selected 76 patients with PD who underwent bilateral STN DBS implantation at the University of Pécs between 2013 and 2015, 1 week before surgery and at postoperative 12 months. Patients were evaluated in on state with standard antiparkinsonian medication. The amount of dopaminergic medication was expressed as levodopa equivalent dose (LED) All patients met the UK Brain Bank criteria for Parkinson's disease, major cognitive deficit was an exclusion criterion. As approved by the Regional and Institutional Research Ethics Committee (3617.316-24983/KK41/2009), all patients also expressed their willingness to participate in the study in writing.

Scales used

The severity of PD symptoms was assessed using the Hungarian validated version of Movement Disorders Society Unified PD Rating Scale (MDS-UPDRS). The presence and severity of dyskinesia were measured by using the validated Hungarian UDysRS and patient diaries. For the general evaluation of non-motor symptoms, the Non-Motor Symptoms Scale (NMSS) was used, in addition, the validated Hungarian PDSS-2 was used to assess the presence and severity of sleep disturbances at night, and the Epworth Sleepiness Scale (ESS) was used to estimate daytime sleepiness. In addition, the presence of depression was analysed separately

using the Montgomery-Asberg Depression Rating Scale (MADRS). Cognitive performance was detected using the Montreal Cognitive Assessment (MoCA), the Mattis Dementia Rating Scale (MDRS) and the Addenbrooke's Cognitive Examination (ACE) scales. Health-related quality of life was assessed using the Parkinson's disease-specific PDQ-39 validated in Hungary and the EuroQol EQ-5D.

Statistics

Statistical analysis was performed using the IBM SPSS software package (version 23.0.2, IBM Inc, Armonk, NY, USA). Since the parameters studied followed a normal distribution, non-parametric tests were used and results are presented with standard deviation (SD). Paired t-test was used to compare differences between baseline and 1-year follow-up. McNemar's test was used to test for dichotomous variables (e.g., the absence or presence of sleep problems and the use or non-use of levodopa). The level of statistical significance was defined as $p<0.05$. The magnitude of the change that occurred was characterised by the effect size index (effect size), or relative to the minimum clinically important difference (MCID) where possible.

5.4 Results

We completed the protocol in 71 patients (52 males, mean age 58.6 ± 9.1 years, 47 patients with rigid-kinetic form and 24 patients with mixed-type PD). 5 patients withdrew their informed consent and their data were not processed.

The MDS-UPDRS total score increased from 76.5±24.3 to 60.4±21.4 ($p<0.001$). One-year follow-up after DBS surgery showed that 25 patients had resolved dyskinesia and 19 had only mild dyskinesia. The UDysRS total score decreased from 38.0±17.8 to 10.8±13.0 ($p<0.001$). In addition, a significant score reduction was observed in all four parts of the UDysRS with STN DBS treatment, with a large effect size in all cases.

When analysing patient diaries, we observed a significant increase in ON time without dyskinesia, and an average reduction in OFF time of 3.5 h. This suggests a clinically relevant reduction in dyskinesia severity and movement limitation due to dyskinesia.

Despite a reduction in antiparkinsonian medication for all patients, from a mean levodopa equivalent dose of 1201.7 ± 568.7mg to 561.8 ± 437.2mg ($p<0.001$), all domains of MDS-UPDRS showed significant improvement. The effect of motor and non-motor symptoms on activities of daily living (domains 1 and 2) improved from 2.9 ± 6.7 to 5.2 ± 8.0 ($p < 0.001$),

representing a medium and small effect size index, respectively. The reduction of 7.6 ± 14.0 points ($p < 0.001$) in the Motor Symptom Examination domain (part 3) clearly exceeded the MCID value, with a small effect size index. However, the significantly better results obtained in the Motor Complications domain (part 4) had a large effect size index, i.e. this improvement can be considered not only statistically but also clinically significant and consistent with what is expected from international data.

Significant improvements in quality of life were detected for both quality of life scales. For the PDQ-39 SI, the mean reduction was 7.2 ± 12.1 points, 4.5 times greater than the MCID threshold (1.6 points). However, the results obtained for both the PDQ-39 and EQ-5D scales have a small effect size index.

With STN DBS treatment, the NMSS total score increased significantly, the non-motor symptoms improved globally. The quality of sleep at night (PDSS-2) and the level of depression (based on MADRS) upgraded significantly. As the improvement in the overall PDSS-2 score exceeded the MCID score (3.44 points), it can be concluded that STN DBS treatment has clinically significant potential to advance sleep quality. In addition, other non-motor symptoms (cardiovascular, memory, autonomic, other problems) improved only tendentiously. Although a significant reduction in MADRS total score reached the MCID threshold (1.9), the NMSS mood domain did not reflect this change.

5.5 Discussion

Our results were congruent with the UdysRS and the MDS-UPDRS Motor Complications Examination and Patient Diary. But the MCID (Minimal Clinically Imontrant Difference) threshold was only reached by the 3rd part of the UDysRS. However, the results obtained in all 4 parts of the UDysRS have a statistically large effect size. (Cohen's d values.)

Not only did the severity of dyskinesia as measured by the UDysRS and its impact on quality of life decrease, but also the number of patients experiencing dyskinesia fell (overall 25 patients 100% -> 64.8%), with a further 19 patients having only mild dyskinesia. After 1 year of follow-up, 62% of patients had no or only mild dyskinesia. In contrast to pallidal DBS treatment, which has an active effect on dyskinesia, STN DBS treatment do not act actively on dyskinesia. In fact, it can induce hypermobility even in off state. The dyskenisa reduction is attributed to LED reduction. The difference between the MADRS and the NMSS mood disorder part suggests that STN DBS treatment has a greater effect on both depression and anxiety.

As a secondary endpoint, our data support that non-motor symptoms and motor complications and the impact of non-motor and motor symptoms on life functioning also improved. Our data are consistent with results from the few previous STN studies using the MDS UPDRS.

5.6 Conclusions

The UDysRS alone assesses the impact of on and off dyskinesia on activities of daily living, independent of other PD symptoms. Treatment with subthalamic DBS not only reduces the degree of dyskinesia but also improves quality of life. We recommend the future use of UDysRS in DBS and LCIG studies. Further research is needed to define exactly which demographic and disease-specific factors determine the anti-dyskinesia effect of STN-DBS treatment.

6. Comparison of subthalamic nucleus target coordinates with 1 and 3 Tesla MRI scans in planning deep brain stimulation surgery

6.1 Introduction

Immediately before DBS surgery, a stereotaxic frame is placed on the patient's head, followed by a special MRI scan. Using the images obtained, the neurosurgeon uses navigation software to identify a target area of a few mm diameter for STN and plans an electrode penetration route that avoids the eloquent areas, lateral ventricles and sulci. If this electrode is sub-optimally positioned, stimulation can easily spread to surrounding structures, causing side effects. In the case of STN stimulation, stimulation extending to the internal capsule can cause dysarthria and tetany.

During deep brain stimulation surgery, targeting error can occur due to several factors: (1) inaccuracy of the targeting frame, (2) displacement of the brain during surgery, (3) CT/MRI fusion error, and (4) geometric distortion in the magnetic field. Aiming errors can be several millimetres off the designated target.

MRI scanning is an excellent tool to delineate deep brain target areas, as the target structures can be morphologically well visualized. However, a shortcoming of the MRI method is geometric distortion, which can lead to inaccuracy in image planning. In addition, increasing the magnetic force fields can lead to further distortion of the image information. This

circumstance may result in the target structure seen in the MRI image not being located exactly in the area we have designated in reality. This circumstance may lead to inaccuracy of morphological deep brain targeting and consequently to stimulation-induced side effects and possibly therapeutic ineffectiveness.

6.2 Targeting

The aim of our study was to compare the stereotaxic target coordinates of the target areas (STN) automatically provided by the planning software with our direct morphological target assignment at different magnetic field strengths (1 and 3T) in the same patient during the planning of deep brain stimulation surgery. By mathematical analysis of the coordinate data, we wanted to investigate whether differences in target coordinates could be detected in the same patient in magnetic fields of different strengths. We also investigated whether there is a difference in target coordinates between targets provided by the planning navigation software and those assigned by the direct morphological method.

6.3 Methods

Six patients with advanced Parkinson's disease (2 male, 4 female, mean age ± standard deviation (SD) 60 ± 20.7 years, mean disease duration 10.5 years ± 4.3 years) were studied preoperatively. The studies were performed with the permission of the local Ethics Committee (case file number 2009/3491).

Patients were examined and indications for surgery were established at the Department of Neurology in Pécs. The MRI scans were performed at the Diagnostic Centre of Pécs, while targetting and the surgical procedures were performed at the Departmetn of Neurosurgery in Pécs. The examinations took place in 2009, when the 1T (Siemens Magnetom Harmony) and the newly installed 3T (Siemens Magnetom Trio) MRI machines were operated in parallel for one month.

The images obtained during the tests were uploaded on CD to the Medtronic Stealth-Station, Treon Plus, Framelink 4 navigation planning system. In all patients, MRI scans were performed in both magnetic fields (1T and 3T). The T1 (MPRAGE) sequence was used to directly visualize anatomical structures (AC, PC), while the T2 sequence was used to directly visualize subthalamic nuclei. CRW Radionics Burlington Ma. stereotaxic aiming device, Radionics Lumina MR stereotaxic frame was used for the operations.

The readout accuracy (rodmarking accuracy) of the reference points of the MRI localization frame in two magnetic fields of different strengths (1T and 3T) was investigated and recorded. We manually marked the anatomical location of AC, and PC on 3D T1 weighted (MPRAGE) sequences in the navigation system. Knowing the location of the AC and PC points, the planning software automatically calculated and provided the intercomissural distance (ICD). Knowing the intercomissural distance, the navigation software automatically (Aut) provided the target coordinates of our selected deep brain target structure (STN) on both sides (Aut STN AP, Lat, Vert).

Using 3D T2 weighted sequences in the subthalamic nuclei, we also assigned the desired target areas within the nucleus on both sides (Man STN AP, Lat, Vert) by direct visualization (Man) in the two magnetic fields of different strengths. In all cases, the assignment of the target region to be investigated based on direct visualization was performed using the same method.

Statistics

The mathematical data of the coordinates determined in 1T and 3T MR were subjected to statistical comparison tests. Since the coordinates calculated in the AP, vertical and lateral planes of the AC, PC and sub-talamic nucleus did not follow a normal distribution, we evaluated the differences using a non-parametric Mann-Whitney test.

6.4 Results

Statistical analysis showed that although differences in the AC, PC coordinates, AC-PC distance, in addition to the left and right STN coordinates automatically assigned (Aut) by the design software and directly visually assigned (Man) were detected when comparing the 1T and 3T test results, these differences were not significant (Mann-Whitney test, $p>0.05$). However, when comparing the reading accuracy (accuracy) obtained when assigning reference points in the MR localization frame, a significant difference ($P<0.01$) was found in the 1T and 3T magnetic fields. This value was higher in the stronger magnetic field (3T accuracy mean ± SD: 0.8±0.3 mm) than in the weaker magnetic field (1T accuracy mean ± SD: 0.4±0.2 mm).

We also examined the differences between coordinate data in 1T and 3T field strength. For the AC-PC distance, this is (mm mean ± SD): 4.4 mm ±0.7 mm, in AC coordinates: 1.8 mm ± 1.7 mm, in PC coordinates: 1.6 ±1.0 mm, in STN coordinates automatically entered by the design software (Aut) on the left side: 1. 5 mm, ± 1.1 mm, right side: 1.9 mm, ± 1.1 mm,

and in the directly visually assigned (Man) left coordinates: 1.5 mm, ± 1.1 mm, right coordinates: 1.9 mm ± 1.6 mm.

The results indicate that a difference of 1.5-1.9 mm in the coordinate data of the two target assignments in the magnetic field under investigation was detected for both the automatically assigned (Aut) and the directly visually assigned (Man) target assignments.

6.5 Discussion

It is well known that the stronger the magnetic field, the better the quality of the image of the target structure. However, an increase in magnetic field strength also leads to an increase in geometric distortion. To avoid distortion, CT/MRI fusion was introduced to eliminate geometric distortion inaccuracy, but it has also been shown that fusion alone can cause geometric error. The above shortcomings in imaging are the reason why deep brain stimulation targeting in clinical practice is mostly multimodal (direct targeting by MRI imaging, intraoperative microelectrode information, and intraoperative electrical stimulation).

T2-weighted MRI sequences have been shown to be suitable for direct visualization of the subthalamic nuclei,. In our study, we sought to answer the question whether, using the same stereotaxic targeting frame, same MRI localization frame, scanning the same patients in 1T and then 3T magnetic fields, and then directly visualizing the subthalamic nuclei with T2 weighted sequences, then targeting them with the same navigation system, a difference in target coordinates in the two different strength magnetic fields can be detected. So far, no relevant data have been found in the literature.

Novotny et al, compared the extent of magnetic field-induced distortion in stereotaxic planning in 1T and 1.5T MR. They found that in 1T the target coordinate discrepancy due to torsion did not exceed 0.6 mm in the axial plane and 0.9 mm in the coronal plane. In the same planes, when tested in 1.5 T, the torsion was 1.0 mm and 1.3 mm. The type of image sequence affected the degree of distortion in both fields of view. When examining the subthalamic core, the T2-weighted spin-echo sequence in the coronal plane caused the largest distortion. This was 2.6 mmm for 1T and 3.0 mm for 1.5 T. Others have investigated the magnetic field targeting inaccuracy caused by torsion in 3T MR. It was found that the distortion-induced target pointing inaccuracy was no greater than 0.132 mm, suggesting that its significance is negligible in DBS surgery planning.

Geometric distortion is more significant in anatomical structures located more peripherally (>1 mm) than in central structures closer to the midline (<1 mm) (10). In our study, we found a significant difference in reading accuracy comparing the reference points of the MR localization frame (located more peripherally around the skull compared to the central location of the STN) in magnetic fields of different strengths. A higher number indicates lower accuracy. This reading accuracy was found to be lower in the stronger magnetic field (0.4 mm in 1T, 0.8 mm in 3T).

It was found that during DBS surgical planning in patients with PD, direct STN targeting with MRI coincided with the final electrode location in 80% of cases. However, intraoperative electrophysiological information (microelectrode registration and intraoperative stimulation) modified the final target assignment to the target initially determined by MRI in about 20% of cases.

6.6 Conclusions

Our present results suggest that there was a difference of 1.5-1.9 mm in the coordinate data of both direct morphological (Man) and indirect (Aut) target assignments performed in the two MRI fields studied (1T and 3T), but this difference was not significant. As the final placement of electrodes during surgery is not exclusively morphological and is significantly modified by intraoperative microelectrode and electrostimulation information, these two latter modalities may be able to compensate for the few millimetres of variation caused by magnetic field distortion.

7. Publications

Impact factor of publications on which the thesis is based: 6,396

Cumulative impact factor: 60.808

Independent citations (MTMT): 67

H-index: 6

7.1 Publications on which the thesis is based:

1. How efficient is subthalamic deep brain stimulation in reducing dyskinesia in Parkinson's disease? Juhász A, Deli G, Aschermann Zs, Janszky J, Harmat M, Makkos A, Kovács M, Komoly S, Balás I, Dóczi T. Büki A, Kovacs N, European Neurology, Ms. No.: 201611008, Section: Original Paper (2017) Q3 IF:1.562
2. Levodopa/carbidopa intestinal gel can improve both motor and non-motor experiences of daily living in Parkinson's disease: an open-label study Juhász A, Aschermann Zs, Ács P, Janszky J, Kovács M, Makkos A, HarmatM, Tényi D, Karádi K, Komoly S, Takáts A, Tóth A, Nagy H, Klivényi P, Dibó Gy, Dézsi L, Zádori D, Annus Á, Vécsei L, Varannai L, Kovács N PARKINSONISM AND RELATED DISORDERS (2017), http://dx.doi.org/10.1016/ j.parkreldis. Q1, IF:4.721
3. A subthalamicus mag célkoordinátainak összehasonlítása 1 es 3 Tesla MR vizsgálattal mély agyi stimulációs műtetek tervezése során Juhász A, Kovács N, Perlaki G, Büki A, Komoly S, Köver F, Balás I IDEGGYÓGYÁSZATI SZEMLE SZEMLE / CLINICAL NEUROSCIENCE (2018) Nov 30;71(11-12):405-410. doi: 10.18071/isz.71.0405. Q4, IF:0.113

7.2 Conference lectures and poster presentations relatetd to the thesis:

1. How Efficient Is Subthalamic Deep Brain Stimulation in Reducing Dyskinesia in Parkinson's Disease? Juhász A, Deli G, Aschermann Zs, Janszky J, Harmat M, Makkos A, Kovács M, Komoly S, Balás I, Dóczi T. Büki A, Kovacs N – poszter presentation - 49th International Danube Symposium, Budapest 2017.04.21-22.
2. Levodopa/carbidopa intestinal gel can improve both motor and non-motor experiences of daily living in Parkinson's disease: an open-label study Juhász A, Aschermann Zs, Ács P, Janszky J, Kovács M, Makkos A, HarmatM, Tényi D, Karádi K, Komoly S, Takáts A, Tóth A, Nagy H, Klivényi P, Dibó Gy, Dézsi L, Zádori D, Annus Á, Vécsei L, Varannai L, Kovács N – lecture - 49th International Danube Symposium, Budapest 2017.04.21-22.
3. A levodopa/carbidopa intesztinális gél kezelés hatékonysága: a magyar Duodopa regiszter egy éves eredményei Juhász A, Aschermann Zs, Ács P, Janszky J, Kovács M, Makkos A, HarmatM, Tényi D, Karádi K, Komoly S, Takáts A, Tóth A, Nagy H, Klivényi P, Dibó Gy, Dézsi L, Zádori D, Annus Á, Vécsei L, Varannai L, Kovács N – lecture – Annual Meeting of Hungarian Scientific Parkinson Society 2017, Visegrád, 2017.05. 26- 27.
4. Milyen hatékony a mély agyi stimulációs kezelés a diszkinézia kezelésére? Juhász A, Deli G, Aschermann Zs, Janszky J, Harmat M, Makkos A, Kovács M, Komoly S, Balás I, Dóczi T. Büki A, Kovacs N – lecture – Annual Meeting of Hungarian Scientific Parkinson Society 2017, 2017.05.26- 27.
5. Levodopa/carbidopa intestinal gel can improve both motor and non-motor experiences of daily living in Parkinson's disease: an open-label study Juhász A, Aschermann Zs, Ács P, Janszky J, Kovács M, Makkos A, HarmatM, Tényi D, Karádi K, Komoly S, Takáts A, Tóth A, Nagy H, Klivényi P, Dibó Gy, Dézsi L, Zádori D, Annus Á, Vécsei L, Varannai L, Kovács N – poszter presentation - 3rd Congress of European Academy of Neurology Amsterdam, 2017.06. 24-27.

7.3 Other publications:

1. Association of myasthenia gravis with polymorphisms in the gene of histamine N-methyltransferase Kellermayer B; Polgar N; Pal J; Banati M ; Maasz A; Kisfali P; Hosszu Z; Juhasz A; Jensen HB; Tordai A et al. HUMAN IMMUNOLOGY 74 : 12 pp. 1701-1704. , 4 p. (2013) IF: 2,282

2. Levodopa/carbidopa intestinal gel can improve both motor and non-motor experiences of daily living in advanced Parkinson's disease Kovacs N; Juhasz A; Aschermann Z; Janszky J; Kovacs M; Harmat M; Karadi K; Makkos A; Takats A; Toth A et al. JOURNAL OF THE NEUROLOGICAL SCIENCES 381 : Supplement pp. 123-124. Paper: 354 , 2 p. (2017) IF:2.448

3. Are the MDS-UPDRS-based composite scores clinically applicable? Kovacs N; Juhasz A; Makkos A; Kovacs M; Harmat M; Aschermann Z; Janszky J; J.EUROPEAN JOURNAL OF NEUROLOGY 25 pp. 247-247. , 1 p. (2018) IF: 4.387

4. Comparing Sensitivity and Specificity of Addenbrooke's Cognitive Examination-I, III and Mini-Addenbrooke's Cognitive Examination in Parkinson's Disease Lucza T; Ascherman Z; Kovacs M; Makkos A; Harmat M; Juhasz A; Janszky J; Komoly S; Kovacs N; Dorn K et al. BEHAVIOURAL NEUROLOGY 2018 Paper: 5932028 , 9 p. (2018) IF: 1.908

5. Applications of the European Parkinson's Disease Association sponsored Parkinson's disease composite scale (PDCS). Balestrino R; Hurtado-Gonzalez C A; Stocchi Fabrizio; Radicati F G; Chaudhuri K R; Rodriguez-Blazquez C; Martinez-Martin P; PDCS European Study Group (Kollaborációs szervezet); Adarmes A D (Kollaborációs közreműködő); Méndez-Del-Barrio C (Kollaborációs közreműködő), Juhász A, et al. NPJ PARKINSONS DISEASE 5 Paper: 26 , 7 p. (2019) IF: 6.75

6. Extensive validation study of the Parkinson's Disease Composite Scale Martinez-Martin P; Radicati FG; Rodriguez Blazquez C; Wetmore J; Kovacs N, PTE/ÁOK/Neurológiai Klinika; PTE/KCS/MTA-PTE Klinikai Idegtudományi Képalkotó Kutatócsoport ; Chaudhuri KR; Stocchi F, Kollaborációs szervezet: PDCS European Study Group, Kollaborációs közreműködő: Vuletic V; et al. (41) EUROPEAN JOURNAL OF NEUROLOGY (1351-5101 1468-1331): 26 10 pp 1281-1288 (2019) IF: 4.516

7. Long-term successful treatment of chronic inflammatory demyelinating polyneuropathy-like polyneuropathy induced by levodopa-carbidopa intestinal gel with intravenous immunoglobulin, Pintér D; Deli G; Juhász A; Pál E; Janszky J; Kovács N; EUROPEAN JOURNAL OF NEUROLOGY 26 : 12 pp. e96-e97. (2019) IF: 4,516

8. Screening for problematic internet use may help identify impulse control disorders in Parkinson’s disease Kovács M; Makkos A; Pintér D; Juhász A; Darnai G; Karádi K; Janszky J; Kovács N, BEHAVIOURAL NEUROLOGY (2019) Paper: 4925015 , 8 p. (2019) IF: 2.093

9. Interleaving stimulation mode can improve better the health-related quality of life in primary generalized or segmental dystonia than standard bilateral pallidal deep brain stimulation Kovács N; Balás I; Pintér D; Juhász A; Harmat M; Vörös V; Janszky J; JOURNAL OF THE NEUROLOGICAL SCIENCES 405 : S p. 30 Paper: UNSP 103929 (2019) IF: 3.115

10. Előrehaladott Parkinson-kór kezelési lehetőségei az optimális terápia kiválasztásának szempontjai Kovács N; Aschermann Zs; Juhász A; Harmat M; Pintér D; Janszky J IDEGGYOGYASZATI SZEMLE / CLINICAL NEUROSCIENCE 72 : 1-2 pp. 5-11. , 7 p. (2019) IF 0.337

11. Trimetazidine and parkinsonism: a prospective study Pintér D; Kovács M; Harmat M; Juhász A; Janszky J; Kovács N; PARKINSONISM AND RELATED DISORDERS 62 pp. 117-121. , 5 p. (2019) IF: 3.926

12. The Impact of Trimetazidine on Disease Severity and Quality of Life in Parkinson's Disease Pintér D; Juhász A; Harmat M; Janszky J; Kovács N; SCIENTIFIC REPORTS 10 : 1 Paper: 10050 , 6 p. (2020) IF: 4.38

13. Relationship between impulse control disorders and preexisting type 2 diabetes mellitus in drug naïve parkinson's disease patients Kovács M; Pintér D; Makkos A; Juhász A; Darnai G; Janszky J; Wittmann I; Kovács N. PARKINSONISM AND RELATED DISORDERS 79 : Suppl 1 pp. e19-e20. (2020) IF: 4.891

14. Trimetazidine treatment in Parkinson's disease: is it a real problem or just a flame? Pintér D; Kovács M; Juhász A; Harmat M; Janszky, J; Kovács N PARKINSONISM AND RELATED DISORDERS 79 p. e75 (2020) IF: 4.891
15. The impact of trimetazidine on disease severity and quality of life in Parkinson's disease Pintér D; Juhász A; Harmat M; Janszky J; Kovács N SCIENTIFIC REPORTS 10 : 1 Paper: 10050 , 6 p. (2020) IF: 4.38
16. Which scale best detects treatment response of tremor in parkinsonism? Pintér D; Forjaz M J; Martinez-Martin P; Rodriguez-Blazquez C; Ayala A; Juhász A; Harmat M; Janszky J; Kovács N JOURNAL OF PARKINSONS DISEASE 10 : 1 pp. 275-282. , 8 p. (2020) IF: 5.568
17. DBS-műtéttel kezelt Parkinson-kóros betegek kézügyesség-javulásának objektív mérése Szántó I; Sándor B; Katona K; Nagy M; Juhász A; Balás I IDEGGYOGYASZATI SZEMLE / CLINICAL NEUROSCIENCE 73 : 7-8 pp. 255-259. , 5 p. (2020) IF: 0,427

7.4 Other conference lectures and poster presentations:

1. Disztónia kezelése mély agyi stimulációval Juhász A; Aschermann Z; Balás I; Kovács N -case presentation - Annual Meeting of Hungarian Scientific Parkinson Society 2015, Budapest, 2015.09.11-12.
2. Mélyagyi stimuláció Fragilis-X,Tremor, Ataxia szindrómában Juhász A; Deli G; Balás I; Aschermann Z; Hadzsiev K; Komoly S; Dóczi T; Büki A; Kovács N – case presentation - Annual Meeting of Hungarian Scientific Parkinson Society 2016, Budapest, 2016.06.03-04.
3. Mély agyi stimuláció hatékonysága esszenciális tremor kezelésében, Juhász A; Balás I; Makkos A; Pintér D; Kovács M; Aschermann Zs; Kovács N -előadás- Annual Meeting of Hungarian Scientific Parkinson Society 2018, Visegrád, 2018.06.01-02.
4. Repetitive transcranial magnetic stimulation can improve anxiety in Parkinson's disease: a randomized, double-blind and controlled trial Juhász A; Makkos A; Kovács M; Harmat M; Pintér D; Kovács N – poster presentation - XXIV. World Congress of Neurology, Dubai, Arab Emirates, 2019.10.27-31.
5. Kufor-Rakeb Syndrome due to a new ATP13A2 mutation, Case report – abstract - Juhász A; Harmat M; Pintér D; Kovács M; Kovács N EUROPEAN JOURNAL OF NEUROLOGY 27: Suppl1 p. 896 (2020)
6. ATP13A2 mutációhoz köthető fiatalkori parkinsonizmus – Kufor-Rakeb szindróma esetismertetés Juhász A; Pintér Dávid, Harmat M; Kovács M; Aschermann Z; Karádi K; Hadzsiev K; Melegh B; Kovács N – case presentation- Annual Meeting of Hungarian Scientific Parkinson Society 2021, 2021.05.28-29.
7. A receptor affinitás szerepe: kedvező hatások a hangulat, kognitív tünetek, neuropathiás fájdalom tekintetében, Juhász A – lecture- Annual Meeting of Hungarian Scientific Parkinson Society 2021, 2021.05.28-29.
8. Problémaorientált gyakorlatias esetbemutatás: Mit lehetett volna jobban csinálni? Juhász A; Aschermann Z; Harmat M; Pintér D; Kovács N – case presentation - Hungarian Scientific Parkinson Society, Parkinson Training Meeting, Gárdony, 2021.09.03-04.
9. Régi történet új köntösben: tapasztalatok a subcutan apomorfin kezeléssel Parkinson kórban Juhász A; Aschermann Z; Harmat M; Pintér D; Kovács M; Karádi K; Kovács N, - előadás - lecture- Annual Meeting of Hungarian Scientific Parkinson Society 2022, Visegrád, 2022.05.27-28.
10. GuideXT a klinikai gyakorlatban - Juhász A; Aschermann Zs; Izsó L; Balás I; Nagy M; Berta B; Kovács N; Pintér D - előadás - lecture- Annual Meeting of Hungarian Scientific Parkinson Society 2022, Visegrád, 2022.05.27-28.

11. Subcutan apomorfin kezelés Parkinson kórban Juhász A, Aschermann Z, Harmat M, Pintér D, Kovács M, Karádi K, Kovács N - lecture - Hungarian Scientific Parkinson Society, Parkinson Training Meeting, Gárdony, 2022.09.02-03.

8 Acknowlegdements

I would like to express my gratitude to both of my supervisors. Whithout the expertise of Prof. Dr. Norbert Kovács this thesis could not have been accomplished. Over the past years working with him, I have learned the professional approach to clinical examination of movement disorders. I would like to thank Dr. Istváni Balás, associate professor for a lot of help, as well as for the exceptional work he performed during deep brain stimulation surgeries.

I am grateful for their support to Prof. Dr. Janszky József, Head of the Department of Neurology, Head of the Doctoral School of Clinical Neurosciences, and to Prof. Dr. Komoly Sámuel former Head of the Department of Neurology, former Head of the Doctoral School of Clinical Neurosciences.

I would like to thank Éva Balázs and Katalin Takács, PD nurses at the time of publications, for their precise and conscientious work with PD patients.

I am thankful to Prof. Dr. Kázmér Karádi and Márton Kovács, clinical psychologist for their work in implementation and evaluation of neuropsychological and neurocognitive tests, and to Dr. Gabriella Deli assistant professor for her help with the intraoperative microelectrical registration during deep brain stimulation surgeries.

I would also like to thank all the employees of the Department Neurology and the Department of Neurosurgery who helped me in my work.