

# Electrophysiological investigations in neurosurgically treated movement disorders

Ph.D. thesis

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## Abbreviations

AD	Analog-to-digital conversion or analog-to-digital converter
DBS	Deep brain stimulation or deep brain stimulator
DBS-OFF	State when the deep brain stimulation is turned off
DBS-ON	State when the deep brain stimulation is turned on
EEG	Electroencephalography
EMG	Electromyography
ERPs	Event-related potentials
ET	Essential tremor
GPI	Internal segment of globus pallidus
HFS	High-frequency stimulation
MRI	Magnetic resonance imaging
PD	Idiopathic Parkinson's disease
sEMG	Surface electromyography
STN	Subthalamic nucleus
TR	Tremor reduction, the quotient of preoperative and postoperative tremor intensity
UPDRS	Unified Parkinson's Disease Rating Scale
Vim	Ventral intermediate nucleus of thalamus

## Introduction and aims

Owing to the introduction of stereotactic functional neurosurgical techniques, several, previously uncontrollable degenerative disorders have become treatable. Both the lesioning (ablation) and the high frequency stimulation (HFS) of certain deep brain nuclei with pathological over-activity may result in improvement of symptoms.

During **ablation**, first a temporary thermocoagulation (40 Celsius) and subsequently permanent lesion (60 Celsius) is performed over the surgical target. Therefore, the physical destruction of pathologically overactive areas results in symptomatic relief in case of ablative treatment. Because these lesions also affects the white matter (e.g. corticobulbar tracts) to some extent, bilateral ablative procedures quite often produce dysphagia, dysarthria and other permanent side-effects.

Conversely, during HFS, **high-frequency (>100 Hz) stimulation** is initiated over the target area resulting in functional inhibition by the means of implanted electrodes. Because HFS does not produce large destructions in the brain, the functional inhibition may be stopped anytime by switching off the stimulation. Therefore, HFS is considerably safer, but more expansive method to treat certain movement disorders and psychiatric conditions than ablation. Further advantage is that the stimulation settings may be adapted later to obtain the optimal efficacy. Most of the side-effects related to HFS may be treated by changing the stimulation parameters and permanent morbidity develops quite rarely.

Clinically HFS can be obtained by the implantation of deep brain stimulator (DBS). The indications for DBS are continuously growing: currently the Food and Drug Administration approved this technique for the treatment of tremor, Parkinson's disease (PD), obsessive-compulsive disorders and dystonia. Furthermore, it seems to be a promising tool for the improving certain epileptic disorders, neuropathic pain, Gilles de la Tourette's syndrome and tardive dyskinesias according to preliminary studies.

To this time there are three conventional targets to treat various types of movement disorders. These targets play different pathophysiological roles; therefore, either the ablation or the HFS of these deep brain nuclei has different clinical consequences.

1. **Ventral intermediate nucleus of thalamus (Vim).** The ablation (thalamotomy) or the DBS of Vim has been shown to markedly improve several types of tremor. Although, it also improves Parkinsonian tremor, this does not significantly improve other features of PD, such as rigidity, bradykinesia, and dyskinesia. However, Vim is a good target to treat essential tremor.
2. **Internal part of globus pallidus (GPi).** The ablation (pallidotomy) and the GPi DBS have a well demonstrated effect on various motor-related symptoms of PD. Owing to the inefficacy to improve bradykinesia, the higher stimulation voltages required to achieve similar therapeutic effect and the lack of possibility to decrease the dose of antiparkinsonian medication, bilateral GPi stimulation is at disadvantage in treating PD. Nowadays, the stimulation of GPi plays a crucial role in the treatment of various primary and secondary dystonias.

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3. **Subthalamic nucleus (STN).** The ablation (subthalamotomy) and the DBS of STN is the ultimate solution for improving drug-refractory, advanced stage PD. It is the only target which has an impact simultaneously on all cardinal features of PD, the bradykinesia, rigidity and tremor.

Newer surgical targets are approaching; however, the efficacy and safety of these methods are still under investigation. The stimulation of **pedunculopontine nucleus (PPN)** seems to be effective in Parkinsonian gait disturbances and the **ventral oral anterior (Voa)** and **posterior (Vop)** nuclei might improve the Holmes tremor and certain dystonic disorders.

In the Department of Neurology, University of Pécs, with the technical help of Ferenc Nagy and Lóránd Kellényi, I introduced the electrophysiological analysis of tremors in 1999. I also developed software for recording and analyzing simultaneous accelerometric, surface electromyographic, electroencephalographic and video recordings.

The primary aim of my research activity was to analyze various effects of functional neurosurgical surgeries on movement disorders, such as

- evaluating the effects of neurosurgical treatments on various tremor characteristics,
- investigating the possibility of bilateral tremor reductive effect of unilateral thalamic (Vim) deep brain stimulation,
- analyzing the alterations in long-latency event-related potentials during deep brain stimulation, and
- studying the tremor genesis.

## Impact of ablative treatments on tremor characteristics

Learning the pathophysiology of the basal ganglia, introducing the method of target localization based on magnetic resonance imaging (MRI) and applying stereotactic considerably improved the efficacy of functional neurosurgical treatments. Despite careful patient selection and precise target localization, the occurrence of ineffective surgeries after ablative treatments is relatively high: it can exceed 10-15%. Even in the cases of ineffective surgeries, a major clinical improvement can usually be detected during and immediately after the operation and the worsening becomes obvious only after a few weeks.

In the background of the surgical inefficacy, pathophysiological, rather than methodological causes are suspected. The sole introduction of an electrode into a pathologically overactive target area results in temporary clinical improvement, even if no ablation is performed. This phenomenon is called as microlesioning effect. Because there is no available method, which is capable to make distinction between the permanent effects of ablation or the temporary effects of microlesioning-phenomenon, we aimed to find a biological marker to predict the long-term efficacy of ablative treatments as early as possible.

### Materials and methods

#### Patients

The effect of 30 consecutive surgical procedures Parkinson's disease patients was evaluated in prospective, long-term follow-up measurements by using accelerometry (ADXL-105, Analog Devices, USA). All patients underwent functional neurosurgical treatments to relieve tremor between December 2001 and December 2003. The **baseline examination** was carried out 2 days before surgery. "**Short-term**" effect was evaluated by analyzing the postoperative tremor 2 days after the intervention. To examine "**long-term**" effects, recordings were made 3 months postoperatively.

During recordings, subjects were positioned in a straight back chair. Their forearms were pronated and supported at the ulnar styloid process, while wrists were slightly dangling and able to move freely. At each occasion, at least 10-15 minutes long recordings were converted by an A/D converter (Power 1401, Cambridge Electronic Design Ltd., UK) with the sampling frequency of 1 kHz. All subsequent analyses (e.g. artifact removal, digital filtering, and frequency calculations) were performed by using Spike2 software (Cambridge Electronic Devices Ltd., Cambridge, UK). The following parameters were evaluated:

1. **Tremor reduction (TR)**, the postsurgical improvement, was quantified by a relative value:

$$\text{Tremor reduction (TR)} = (\text{preoperative tremor intensity}) / (\text{postoperative tremor intensity}).$$

Consequently, larger TR value indicates more reduction in tremor and better surgical outcome.

2. **Tremor frequency** was determined by autocorrelation.

3. **Surgical outcome** was evaluated 6-12 months after the surgery by two independent investigators either as '**effective**' or '**ineffective**' based on the clinical symptoms

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Mann-Whitney test was applied to test statistical significance because the obtained values did not follow the normal distribution (SPSS v11; SPSS Inc., Chicago, USA). The level of statistical significance was set to 0.05.

## Results

### Evaluation of effective ablative treatments

Twenty-seven operations (90% of all operations) turned to be effective on a long term basis. The intensity of rest tremor became significantly lowered postoperatively ( $p<0.001$ ). Despite of the long-term efficacy, a statistically significant, but clinically irrelevant worsening could be observed between the short- and long-term tremor reduction values (TR: 47.5 vs. 29.6, respectively). (**Table 1**).

Rest tremor frequency increased with 2.2 Hz on an average ( $p<0.001$ ). The type of ablative treatment (pallidotomy vs. thalamotomy) did not have an influence on either the tremor reduction or the frequency increase. (**Table 1**).

Examination	Tremor reduction <sup>a</sup>		Frequency	
	Effective	Ineffective	Effective	Ineffective
Preoperative state	N/A	N/A	5.16 Hz	5.07 Hz
2 days postoperatively	47.5 <sup>b</sup>	53.3 <sup>b</sup>	7.36 Hz <sup>b</sup>	4.99 Hz <sup>c</sup>
3 months postoperatively	29.6 <sup>b</sup>	2.1 <sup>b,c</sup>	7.29 Hz <sup>b</sup>	5.12 Hz <sup>c</sup>

**Table 1. Characteristics of postsurgical rest tremor after ineffective operations compared to effective interventions.** The median values of tremor reduction and tremor frequency are compared between effective and ineffective neurosurgical interventions. For definitions of tremor characteristics and the efficiency of surgery refer to text.

<sup>a</sup>Postoperative tremor reduction is given in a relative value.

<sup>b</sup>Statistically significant change compared to presurgical value ( $p<0.01$ )

<sup>c</sup>Statistically significant difference compared to effective group ( $p<0.01$ )

N/A = not applicable

### Evaluation of ineffective ablative treatments

In three cases, the operation resulted in only a transient improvement, which means 10% of all interventions. On the second postoperative day, the clinical improvement was prominent, the short-term tremor reduction of ineffective treatments did not differ significantly from that of effective operations (TR: 53.3 vs. 47.5,  $p=0.08$ ). However, three months postoperatively the Parkinsonian symptoms reappeared and consequently the long-term TR values also worsened comparing to the short-term (2.1 vs. 53.3). (**Table 1**).

The frequency of rest tremor remained unchanged: Unlike in the case of effective treatments, no frequency increase could be detected comparing to the baseline (frequency change: -0.08 Hz,  $p>0.05$ ). (**Table 1**).

## Discussion

In the present study we compared the effects of effective and ineffective ablative treatments on resting Parkinsonian tremor. The occurrence of ineffective treatments was 10%, which is acceptable according to the literature.

Our study demonstrated that in the cases of effective treatments there is a subclinical worsening in the first three postoperative months. The tremor on the 2<sup>nd</sup> postoperative day and the 3<sup>rd</sup> postoperative month seemed to be the same by physical examination; however, accelerometry detected a significant increase in intensity. This increase in tremor intensity was clinically negligible. In the background, we may postulate the effect of microlesioning-phenomenon, which might give an additional slight and transitory tremor reduction to the short-term effect of ablations. According to our results, the type of ablation (pallidotomy vs. thalamotomy) did not have any influence on either the tremor reduction or the frequency increase.

Interestingly, we could not identify any markers by physical examination to predict the long-term outcome. The postoperative short-term tremor reduction did not differ significantly between effective and ineffective treatments. The fundamental difference between the effective and ineffective treatments was the presence or the absence of frequency changes. While the frequency significantly increased after all effective treatments, it practically remained the same after all ineffective operations.

The frequency of pathological tremors within an individual is quite stable; it changes with only a few tenths of Hertz over years. Consequently, we may assume that the frequency increase observed after successful ablations is probably due to the ablation itself.

Previous studies demonstrated that after DBS the tremor frequency increased to a statistically significant extent. Two theories have been suggested to explain this phenomenon. According to the first theory, DBS itself is able to reset the frequency of certain central oscillator loops. Alternatively, DBS may suppress certain oscillators. Since we observed accelerometrically very similar effects of ablative treatments, suppression rather than resetting oscillators seems more probable.

Several theories suggest that the highly synchronized pathological tremor generators are superimposed on the physiological oscillators. Presumably, if the neurosurgical interventions (either ablations or DBS implantations) destruct the actions of these pathological oscillators, the physiological tremor generators come to the front resulting in higher tremor frequency.

However, **in the case of ineffective treatments**, the pathological oscillators are not destructed permanently, so they can continuously override physiological tremor generators. The unchanged tremor characteristics indicate that postsurgical tremor is still highly synchronized. The clinically well detectable short-term tremor reduction might be due to the microlesion-effect or microedema, which is able to temporarily decrease the intensity of tremor, but is not sufficient to alter other accelerometric properties (e.g. frequency).

To verify that the presence or absence of frequency increase is able to differentiate the effective ablations from the ineffective ones as early as during the operation, further studies are planned. If this method turns to be a useful method with good specificity and sensitivity, it may reduce the occurrence of ineffective surgeries worldwide.

## Bilateral effects of unilateral deep brain stimulation

Unilateral DBS of the ventral intermediate thalamic nucleus (Vim) is a technique widely used to relieve various types of tremor. However, the question of whether this technique exerts exclusively a unilateral or a bilateral tremor-reducing effect remains open.

### Methods

In a search for clinically bilateral effects, we reviewed all cases in which a unilateral Vim DBS had been implanted in the Departments of Neurology and Neurosurgery at the University of Pécs. Among the 16 cases involving thalamotomy and contralateral Vim stimulation, we found only a single case where the unilateral thalamic DBS had clinically improved both the bilateral limb and head tremor. We applied simultaneous surface electromyography (sEMG), accelerometry and video recording in order to evaluate the presence of an active tremor reduction on the nontarget (ipsilateral) side in this specific case.

#### The patient

The 55-year-old woman suffers from tremor related to biopsy-proven mitochondrial encephalomyopathy. At the age of 48, she experienced pharmacoresistant bilateral, predominantly postural-kinetic limb and head tremor and several stroke-like episodes. The tremor affected the right side more seriously. Extensive examinations relating to the possibilities of Wilson's disease, Parkinson's disease, essential tremor, Holmes' tremor, psychogenic tremor and enhanced physiological tremor yielded negative results. As the handicapping bilateral tremor was pharmacoresistant, left thalamotomy and subsequently right Vim DBS implantation were performed. With the stimulating parameters 0-C+, 130 Hz, 60  $\mu$ s, 1.4 V, permanent and pronounced tremor reduction was achieved.

#### Tremor recording

Four years after the DBS implantation, tremor was investigated in resting, postural and kinetic positions. During each session, measurements lasting 2-10 minutes were made with calibrated accelerometers (ADXL-105 and ADXL-320, Analog Devices Inc., USA). For bipolar sEMG, Ag/AgCl electrodes were applied to the belly and the tendon of flexor and extensor forearm muscles.

#### Data analysis

Electrophysiological data and the video recording were investigated simultaneously, similarly to video-EEG technique used in epilepsy monitoring. Technical artifacts were eliminated using Spike2 (version 6.03, Cambridge Electronic Design Ltd., UK). After digital filtering, sEMG recordings were rectified. Three parameters were determined:

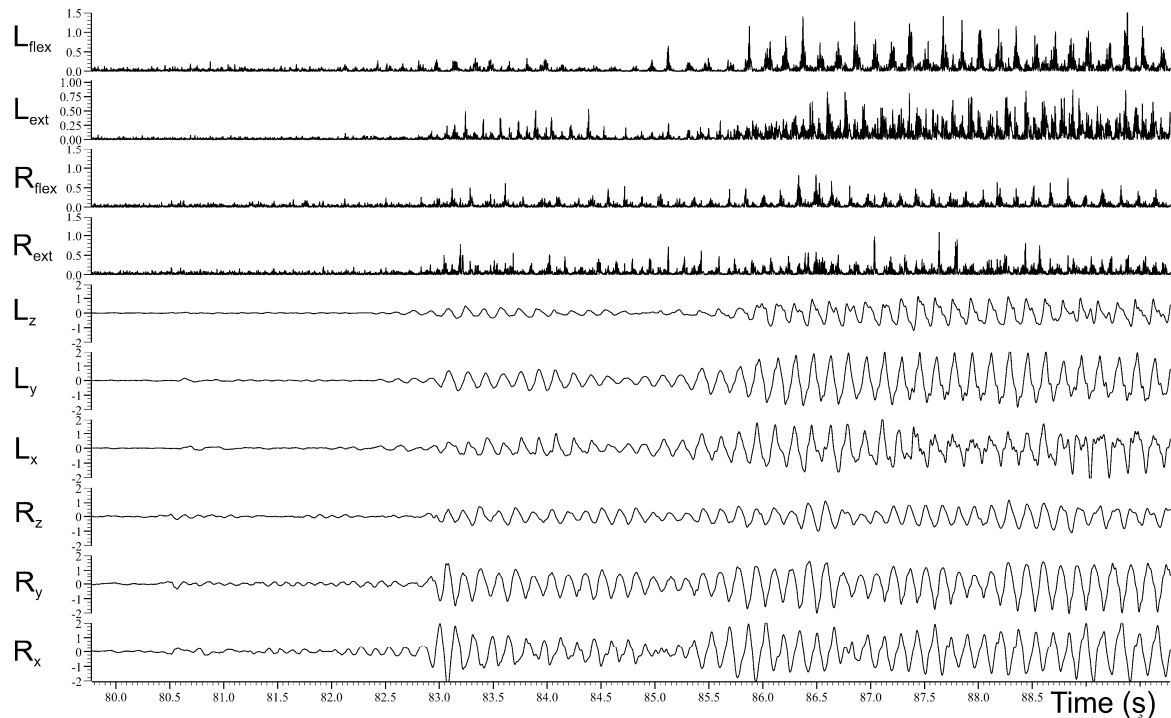
- (1) The **frequency** of tremor was determined by analyzing autocorrelation curve.
- (2) The **intensity of tremor** was calculated by Fast Fourier Transform.
- (3) The **presence or absence of tremor-related bursts** on the sEMG signal was determined by both visual and cross-correlation analysis between the accelerometry and sEMG.



## Results

If the **DBS was turned on**, no tremor could be detected visually in any of the examined positions and tremor-related burst activity was also absent on sEMG recordings.

After the **stimulator was turned off**, however, bilateral limb tremor and head tremor appeared on both sides (**Figure 1**). Furthermore, the intensity of right kinetic tremor was also much higher than that of left (1268 and 889 milli-g<sup>2</sup>, respectively). Switching on DBS abolished the tremor bilaterally.



**Figure 1. A simultaneous accelerometric and rectified surface EMG recording (sEMG) is presented. The right Vim DBS was turned off at 80.5 sec. L=left, and R=right side. In the accelerometric recordings, the indices x, y, z indicates the 3 different planes. Flex and ext denote sEMG of flexor and extensor forearm muscles. One y-axis unit equals with 1 gravity (9.807 m/s<sup>2</sup>).**

## Discussion

A recent paper by Chung and colleagues on the bilateral effects of unilateral subthalamic DBS described an approximately 20% reduction in the ipsilateral subscores of Unified Parkinson's Disease Rating Scale. Their result inspired us to test whether unilateral Vim DBS might have a bilateral tremor-reducing effect. A review of all of our cases, revealed only a single instance, where unilateral thalamic stimulation after contralateral thalamotomy apparently caused clinically pronounced bilateral effects.

The electrophysiological examinations in this unique case indicated that the unilateral DBS definitely reduced the bilateral limb and head tremor:

1. After the right Vim DBS was turned off, moderate rest tremor appeared in both hands and the head. It might be hypothesized that the right-sided rest tremor could be the result of passive, mechanical effects of the left hand tremor, but the bursting of the right forearm muscles contradicts this.
2. While the right hand was carrying out the finger-to-nose maneuvers and the left hand was in the resting position, the kinetic tremor on the nontarget (right) side had a much higher intensity than that on target side. Similarly during writing and spiral-drawing with the right hand, the right kinetic

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tremor was more pronounced than the left rest tremor. Consequently, these right kinetic tremors cannot simply reflect the mechanical overflow from the tremor of the left limbs.

3. When the stimulator was turned on, head tremor also disappeared. Previous studies have clearly demonstrated that bilateral thalamic stimulation is usually required to achieve the most consistent improvement in this symptom.
4. Other previous studies have revealed that Vim DBS increases the tremor frequency. In our case, when the right Vim DBS was switched on, the frequencies of both hands increased.

The physical examination and the electrophysiological data suggest active oscillators behind the right hand tremor, which can be inhibited by the right Vim DBS; therefore, the unilateral Vim stimulation can induce bilateral effects. We cannot explain the exact mechanism underlying this phenomenon, and why it is manifested in only one subject and not in our other 15 patients with unilateral thalamotomy and contralateral Vim DBS. We can merely speculate that the mechanism underlying this phenomenon may be disease-specific (e.g. mitochondrial disorder) in our patient. Alternatively, it may reflect an individual anatomical variation of the interconnections between the two hemispheres, or may be a result of a combination of these mechanisms. The absence of similar phenomenon in the 15 other cases and the relatively low voltage level (1.4 V) used for stimulation may suggest the presence of an individual neuroanatomical constellation.

The better understanding of bilateral effect of unilateral DBS may result in better surgical targets and outcomes, consequently.

## Deep brain stimulation and long-latency event-related potentials

The analysis of long-latency event-related potentials (ERPs) is of importance in the evaluation of certain cognitive functions and in following their subsequent changes. Alternatively, various neuropsychological tests can be applied for a similar purpose, but the severely affected PD patients (especially in an off-medication and off-stimulation state) may experience considerable difficulties in performing such tests. The advantages of applying ERPs rather than neuropsychological tests include the higher reproducibility, the shorter performance time and the lack of possibility of delusion by the subjects.

The aim of the present study was to evaluate whether the deep brain stimulation (DBS) itself can cause any changes in the configuration of the ERPs and in the accuracy of the performance during the oddball paradigm.

### Methods

Twenty-three patients with idiopathic PD participated in the study (age:  $61.3 \pm 5.7$  years, 13 males, disease duration  $8.9 \pm 2.1$  years). In all cases, subthalamic electrodes were implanted bilaterally and optimal therapeutic effect was achieved using unipolar,  $3.10 \pm 0.42$  V, 60  $\mu$ s, 130-135 Hz settings. None of the patients suffered from any other neurological illnesses or dementia, and had not experienced any psychotic episode previously. The control group consisted of 14 subjects ( $62.3 \pm 4.8$  years, 8 males) who did not have any kind of neurological disorder or dementia either. All participants received scores of  $>27/30$  points in the Hungarian version of the Mini-Mental State Examination to exclude dementia.

#### Cognitive ERP recording

Cognitive ERP measurements were carried out at least 6 months (on average  $11.1 \pm 2.9$  months) after implantation, by which time the microlesioning effect had disappeared and the DBS had achieved constant, marked effects in relieving the PD symptoms.

The whole procedure was based on the current guidelines of the International Federation of Clinical Neurophysiology. ERPs were elicited by using a simple discrimination task, the oddball paradigm. Among the frequent (approximately 85%), 2000 Hz, irrelevant (non-target) signals, randomly generated lower tone (1000 Hz), relevant (target) stimuli were played at constant intensity (70 dB hearing level, 50 ms duration). The interstimulus interval varied randomly between 1.5 and 2.5 s. Subjects were asked to press a button immediately after hearing the target signal. The speed and the accuracy of button pressing were equally emphasized; the patients were instructed to press the button as quickly as they could after hearing the target signal, and to avoid button pressing after non-target signals. The calibrated output of an EEG16X (Medicor Inc., Budapest, Hungary) was digitalized at a sampling rate of 1000 Hz, using a CED Power 1401 A/D converter (Cambridge Electronic Devices Inc, Cambridge, UK).

All measurements were carried out after at least 12 hours (usually overnight) drug withdrawal to eliminate the aliasing-effect of dopaminergic therapy on the P300 characteristics. The DBS turned off

(**DBS-OFF**) and DBS turned on (**DBS-ON**) states were evaluated in a random sequence. Recordings were accepted for further analysis only if the online ERP curves were well-configured and reproducible.

### Data analysis

All offline measurements and data modifications were carried out with Spike2 (version 6.03, Cambridge Electronic Devices Ltd, Cambridge, UK). Technical and eye-movement artifacts were first removed by using a semi-automated method under visual guidance.

During ERP calculations, only those target signals were included which were followed by button pressing. Subsequently, the latencies and amplitudes of the P200 and P300 components were determined. In cases of bifurcated P300, P3b components were measured. The reaction time (the interval between the target stimulus and the button pressing), the button pressing time (the interval between the starting and the ending point of button pressing), the percentage of valid signals (the number of target signals followed by button pressing divided by the number of target signals) and occurrence of erroneous button presses (the number of button presses after non-target signals divided by the number of non-target signals) were also calculated. Finally, we correlated these parameters with the disease duration and stimulation amplitude. Since none of the variables were distributed normally, Wilcoxon signed ranks and Mann-Whitney tests were performed. For correlations, Kendall's tau was applied.

## **Results**

### P300 and P200 latencies and amplitudes

Comparison of the results for the control group with those for the DBS-ON or DBS-OFF states demonstrated that the P300 latencies of Cz, Fz and Pz were significantly shorter ( $p < 0.05$ ).

On comparison of the DBS-ON and the DBS-OFF recordings, none of the examined P200 and P300 latency and amplitude parameters was found to exhibit statistically significant differences. However, tendencies were observed to differences between these two states. After the stimulation was turned on, the P300 latencies became slightly shortened and the amplitude increased in some electrode positions (e.g. most midline electrodes: Cz, Pz and Oz, and the central region: C3 and C4), but these changes did not attain the level of statistical significance. Interestingly, in the frontal region (Fz, F8, F7, F3 and F4) the P300 latency was slightly prolonged and the amplitude was decreased after the stimulator was turned on, but likewise to statistically insignificant extents. The P200 amplitudes decreased minimally in the midline positions after the stimulation was initiated.

### Reaction time

The reaction times were significantly longer in the DBS-OFF state than in the DBS-ON state ( $p < 0.05$ ) or in the healthy group ( $p < 0.05$ , **Table 2**).

### Button pressing time

In contrast with our expectations, the duration of button pressing was significantly shorter when the DBS was turned off than it was turned on ( $p < 0.05$ , **Table 2**).

### Percentage of valid signals

In the DBS-OFF state, the patients missed the button pressing after the target signals more often ( $p < 0.01$ , **Table 2**) than during the stimulation.

### Occurrence of erroneous button pressing

In the DBS-OFF condition, the patients erroneously pressed the button after the non-target signals significantly more frequently ( $p < 0.05$ , **Table 2**), than they did in the DBS-ON condition.

Studied task	DBS-OFF			DBS-ON			Control group		
	Median	25 <sup>th</sup> percentile	75 <sup>th</sup> percentile	Median	25 <sup>th</sup> percentile	75 <sup>th</sup> percentile	Median	25 <sup>th</sup> percentile	75 <sup>th</sup> percentile
Reaction time	<b>486 ms</b>	398ms	710 ms	<b>439ms</b>	378ms	527ms	<b>418ms</b>	328ms	489ms
Duration of button press	<b>272ms</b>	243ms	332ms	<b>324ms</b>	293ms	397ms	<b>305ms</b>	285ms	368ms
Percentage of valid signals	<b>95.7%</b>	92.7%	97.1%	<b>98.3%</b>	95.2%	98.6%	<b>98.9%</b>	96.9%	99.2%
Occurrence of mistakenly pressed buttons	<b>1.34%</b>	0.62%	3.48%	<b>0.47%</b>	0.22%	0.70%	<b>0.38%</b>	0.13%	0.68%

**Table 2. Comparison of the choice reaction time, the duration of button pressing, the percentage of valid signals and the occurrence of mistakenly pressed buttons in both the Parkinsonian and the control group. For the Parkinsonian group two states were evaluated: deep brain stimulation turned off (DBS-OFF) and turned on (DBS-ON).**

### Correlation with the stimulation voltage

In the DBS-ON state, the P300 amplitudes over the Cz, F4, C4, F7, F3, T3, C3 and P3 electrodes exhibited a moderate, but statistically significant positive correlation with the stimulation voltage applied (coefficients: 0.41-0.51,  $p < 0.05$ ); the strongest correlation demonstrated in the case of F7 (coefficient: 0.51,  $p = 0.009$ ).

### Correlation with the disease duration

The P300 latencies over Fz, Cz, F8 and P3 during stimulation and over F2 and F3 with the DBS turned off displayed a significant positive correlation with the disease duration. Moreover, the button pressing time in both the DBS-ON and the DBS-OFF conditions correlated with the disease duration (coefficients: 0.43-0.58,  $p < 0.01$ ).

## **Discussion**

Bilateral subthalamic DBS is a technique widely used to treat drug-resistant, advanced idiopathic PD. However, some contradictory data have been reported on the impact of DBS on the cognitive functions. By making use of long-latency ERPs, we set out to test various cognitive factors including attention, memory and speed of stimulus evaluation time. We hypothesized that any impact of DBS on the cognitive processes would result in P300 and P200 amplitude and latency alterations.

The inter-group analysis between the PD patients (either DBS-ON or DBS-OFF) and the control subjects confirmed the previously published data, demonstrating significantly increased P300 latencies in the midline electrode positions. Therefore, the difference in P300 latencies between non-demented, advanced PD patients and age-matched control subjects is a well-established phenomenon.

Our comparison of the ERPs elicited during the DBS-ON and DBS-OFF conditions did not demonstrate uniform, statistically well-established alterations. Neither the amplitude nor the latency of the examined ERP components changed significantly over any electrode position. However, even though statistical significance was not attained, the topographic analysis revealed definitive tendencies: Over most of the midline positions, the P300 latencies slightly shortened, while over the frontal electrodes they became mildly prolonged in the DBS-ON state.

In contrast, the measurements of the behavioral and attentional changes, such as the latency of button pressing or the percentage of missed button pressing and erroneous pressings clearly indicated the positive effects of bilateral subthalamic stimulation: The accuracy and the latency of the button pressing responses to the target signal improved significantly after the DBS was turned on, resulting in fewer erroneous button presses after non-target signals and a shorter reaction time.

Interestingly we observed a moderate positive correlation between the P300 amplitudes (mostly over central and frontal regions) and the optimal stimulation voltage. On the other hand, we also detected a moderate correlation between the disease duration and the P300 latencies. A longer disease duration resulted in longer P300 latencies among others in some midline positions (Cz and Fz) when the DBS was turned on, which may be associated with the more pronounced subclinical cognitive changes produced by the Parkinsonian neurodegeneration.

Few studies have been reported on DBS and cognitive ERPs. Gerschlager, et al. demonstrated that after the DBS was turned on, the reaction time decreased significantly; but the reaction times they observed were much longer than ours (DBS-ON:  $599 \pm 93$  ms; DBS-OFF:  $671 \pm 98$  ms). Similarly to our results, they could not identify significant P300 latency changes after the DBS was turned on; but again, the latencies that they reported were much longer than ours (DBS-ON  $429 \pm 36$  ms; DBS-OFF  $440 \pm 45$  ms). These differences may be explained by several factors: we included considerably more patients (23 vs. 8), whose disease duration (7.1-12.3 vs. 8-22 years) and stimulation settings ( $3.10 \pm 0.42$  Volt,  $60 \pm 0\mu$ s vs.  $2.4 \pm 0.76$  V,  $84.4 \pm 12.1$   $\mu$ s) were more homogeneous. The stimulation mode (unipolar vs. bipolar) and the time interval between the operation and the examination were not mentioned in their manuscript. Furthermore, they compared only the latency of P300 over Cz between the DBS-ON and DBS-OFF states by applying a sampling frequency rate of 250 Hz with a 100 Hz low-pass filter, and a constant interstimulus interval (2 sec), which may also have had an impact on the ERP configuration.

As far as we are aware, our study is the first attempt to compare the topographic distribution of both the latencies and amplitudes of the P200 and P300 components between DBS-ON and DBS-OFF conditions. Unexpectedly, we could not discern a clear-cut, uniform effect of bilateral subthalamic stimulation on the configuration of the cognitive ERPs. However, the attentional and motor performance aspects seem to be changed in response to DBS. Similar to the neuropsychological tests, these results may indicate that deep brain stimulation possibly exerts different effects on different electrophysiological parameters and presumably on different aspects of mental functions, as well. Since the time interval between the operation and the ERP examination was rather short in our case (approximately 1 year), we intend to repeat this investigation on the same subjects with the same protocol, but at 5 years postoperatively.

## Conclusions

Regarding the electrophysiological investigations of various movement disorders, I have made the following progresses:

1. First in Hungary, we have introduced the electrophysiological investigation of tremors as a clinical and scientific tool in the Department of Neurology, University of Pécs in 1999.
2. I have developed a piece of software capable of recording synchronous electrophysiological and video data, and analyze them in a semi-automated fashion. This program is useful not only in the investigation of various tremors, but also in the evaluation of evoked-potentials, eye-movements and heart-rate variability.
3. I was the first who identified a biological marker (namely the frequency increase), which predicts the long-term outcome of ablative neurosurgical treatments. Based on the presence or absence of the frequency-increase, I could identify successful and unsuccessful cases as early as the second postoperative day. These results may help in identifying the inefficiency during the operation, thus can dramatically improve surgical effectiveness.
4. Besides ablative treatments, the consecutive tremor analysis of deep brain stimulation (DBS) also yielded in important results. I was the first to demonstrate the possibility of the bilateral effect of unilateral thalamic (Vim) stimulation.
5. I was the first who evaluated the effects of deep brain stimulation on the topographic distribution of long-latency event-related potentials. I demonstrated that one year after the implantation bilateral subthalamic DBS did not alter the latencies and amplitudes of P200 and P300 components. Conversely, the accuracy of button pressing and the length of choice reaction time were improved after the stimulation was turned on. This phenomenon might indicate a positive impact of the DBS on certain aspects of cognition.

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