Electrophysiological investigations in neurosurgically treated movement disorders

Ph.D. thesis

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Abbreviations

ADC	Analog-to-digital conversion or analog-to-digital converter
AI	Asymmetry index
ApEn	Approximate entropy
CNS	Central nervous system
DBS	Deep brain stimulation or deep brain stimulator
DC(-offset)	Direct current offsetting from the zero
EEG	Electroencephalography
EMG	Electromyography
ERPs	Event-related potentials
ET	Essential tremor
FFT	Fast Fourier Transform
FIR	Finite Impulse Response digital filter
GPi	Internal segment of globus pallidus
HFS	High-frequency stimulation
IIR	Infinite Impulse Response digital filter
mFTMTRS	Modified Fahn-Tolosa-Marin Tremor Rating Scale
MER	Microelectrode recording
MRI	Magnetic resonance imaging
MSE	Multiscale entropy
PD	Idiopathic Parkinson’s disease
PRT	Parkinsonian rest tremor
PS	Power-spectrum
RMS	Root mean square value
sEMG	Surface electromyography
STN	Subthalamic nucleus
T	Tesla
TP	Total power
UPDRS	Unified Parkinson’s Disease Rating Scale
Vim	Ventral intermediate nucleus of thalamus

Introduction and aims

Despite the thorough investigations, tremor remains a mysterious phenomenon in humans. Physiological and pathological tremors have been intensively examined using electrophysiological methods since the mid-sixties; however, their exact purpose and pathomechanism are still unclear.

Pathological tremors are present in most movement disorders, which can usually be controlled by drugs in the beginning of appearance, but which usually becomes more severe and drug-refractory over time. Owing to the introduction of stereotactic ablations and high-frequency stimulation (HFS) techniques, several, previously uncontrollable conditions have become treatable.

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 a software for recording and analyzing simultaneous accelerometric, surface electromyographic, electroencephalographic and video recordings. Beside research, I applied these tools to answer clinical problems, such as

- helping the clinical differential-diagnosis, and
- estimating the effects of drug therapy on tremor reduction.

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 after deep brain stimulation, and
- studying the process of tremor genesis.

Physiological and pathological tremors

The word tremor was derived from the Latin “tremere”, meaning “to tremble.” Tremors may be defined as involuntary oscillations of any part of the body around any plane, with such oscillations being either regular or irregular in frequency and amplitude and resulting from alternating or synchronous action of groups of muscles and their antagonists[1].

Classification of tremors

In the nineties, the use of tremor-related technical terms was controversial, especially the synonymous application of action and kinetic tremor was sometimes misleading. To unify the nomenclature, the following phenomenological and syndromic classification was introduced by the Movement Disorders Society in 1998[2].

Phenomenological classification of tremors

1. **Rest(ing) tremor** occurs in a body part that is not voluntarily activated and is completely supported against gravity. The amplitude of tremor must increase during mental activation (e.g. counting backwards), and diminish during the onset of voluntary activation[2] and reoccur after a certain time period[3].
2. **Action tremor** is present on any voluntary contraction. Depending on the appearance, we can distinguish several subtypes:
   a. **Postural tremor** is present while the body part is maintaining position against the gravity.
   b. **Isometric tremor** occurs as result of muscle contraction against a rigid, stationary object (e.g. against a load).
   c. **Kinetic tremor** occurs during any voluntary movement.
      - **Simple kinetic tremor** is observable during non-goal-directed voluntary movements.
      - **Intention tremor** develops when the amplitude increases during movements toward a target.
      - **Task-specific kinetic tremor** may appear during specific activities (e.g. occupational tremors, primary writing tremor).

Syndromic classification of tremors

Tremors arising from different etiologies may have similar phenomenology. In some cases the phenomenological description of tremor implies a clear-cut etiology, but in most cases describes a syndrome leaving the etiology open.

1. **Normal tremor**
   a. **Physiological tremor** is present during posture and action. The frequency is usually 6-12 Hz, which arises from mostly mechanical oscillations.
   b. **Enhanced physiological tremor** is a visible, predominantly postural, high-frequency tremor (6-12 Hz) without the evidence of a neurological disease. Most important examples are the tremors related to stress or stage fright or hyperthyroidism.
2. **Essential tremor syndromes**
   a. **Classical essential tremor** (ET) is a monosymptomatic, predominantly postural and action tremor, which tends to progress slowly over the years. Prevalence rates vary between 0.4% and 5.6%[4-6]. The clinical diagnostic criteria for ET highly rely on the clinical manifestation of tremor[2, 7, 8].
   b. Variants of essential tremor
      - **Primary writing tremor** has two subtypes: *"task-specific"* tremor appears during writing only *(type A)* and *"position-specific"* tremor develops when the hand position to be used for writing is adopted *(type B)*.
      - **Isolated voice tremor** is diagnosed if tremor is limited to the vocal cords alone. To diagnose the isolated voice tremor, one must exclude the focal dystonia of vocal cords (e.g. spasmodic dysphonia)
      - **Isolated chin tremor** is a quite rare, autosomal dominant disorder, where the high frequency tremor of the mentalis muscles starts in early childhood.
3. **Dystonic tremor syndromes**
   a. **Dystonic tremor** occurs in a body part, which is affected by dystonia (e.g. both the dystonia and tremor affects the same limb).
   b. **Tremor associated with dystonia** specifies a tremor occurring in a body part not affected by dystonia (e.g. a hand tremor in a patient with cervical dystonia).
   c. **Dystonia-gene associated tremor** (e.g. an isolated hand tremor developing in a patient with first-degree relatives with spasmodic torticollis).
4. **Parkinsonian tremor syndromes.** The reason for this classification is that in up to 40% of patients fulfilling the brain bank criteria[9-11] have different forms of postural and action tremor besides the "classical" resting tremor [3, 12, 13].
   a. **Type I or classical Parkinsonian tremor** means either sole rest tremor or resting and postural/action tremor with the same frequency. In the latter case, upon initiation of a voluntary movement the tremor is suppressed, but reoccurs after a few seconds. These kinetic/postural tremor components are considered the continuation of the resting tremor.

   b. **Type II** Parkinsonian tremor means the co-existence of resting and postural/action tremors of different frequencies. It can be considered as the combination of Parkinsonian rest tremor with either enhanced physiological tremor or essential tremor.
   c. **Type III** Parkinsonian tremor refers to isolated postural/action tremor. It is a rare phenomenon, but sometimes does occur in the akinetic rigid variant of Parkinson's disease (PD).
   d. **Type IV.** Monosymptomatic tremor at rest without overt signs of bradykinesia or rigidity can be present, which is not sufficient to fulfill a diagnosis of PD.
5. **Cerebellar tremor** syndromes indicate pure or dominant intention tremor with frequency mainly below 5 Hz. Postural tremor, but no rest tremor, may be present.
6. **Holmes' tremor** (rubral tremor, midbrain tremor or Benedikt's syndrome) is due to a lesion of the central nervous system (CNS), usually in the midbrain. The presence of slow frequency (<4.5 Hz) rest and intention tremor characterizes the disease. If the time of the lesion is known, a delay between the development of the lesion and the first occurrence of tremor can vary between 2 weeks and 2 years.
7. **Palatal tremor** was originally classified as palatal myoclonus. However, because of its rhythmic nature, it has been reclassified as a tremor having two distinct forms:
   a. **symptomatic palatal tremor** (with a preceding brainstem/cerebellar lesion and subsequent olivary pseudohypertrophy)
   b. **essential palatal tremor** (without any obvious CNS lesions).
8. **Drug-induced and toxic tremor syndromes** are considered if the tremor occurs in a reasonable time-frame following drug ingestion. It may have various phenomenological appearance, such as enhanced physiological tremor (e.g. sympathomimetics or antidepressants), Parkinsonian tremor (e.g. neuroleptics or dopamine-receptor blocking drugs), and cerebellar tremor syndromes (e.g. lithium).
9. **Tremor syndromes in peripheral neuropathy** are predominantly of postural and action types. Dysgammaglobulinemic neuropathies, Guillain-Barré syndrome and chronic inflammatory demyelinating neuropathies are the most common disorders eliciting neuropathy-induced tremor.
10. **Psychogenic tremor syndromes** have different clinical pictures. The sudden onset and remission of the condition, the clinical combination of resting and postural/intention tremor, the decrease of tremor amplitude during distraction, the variation of tremor frequency during distraction or contralateral voluntary movements, the presence of coactivation sign and the psychosomatic disorder in the patient's history suggest the diagnosis of psychogenic tremor.

Tremor genesis

The exact purpose of physiological tremor is still unknown; however, it is thought to help keep the stand-by condition of the striated musculature. Four different mechanisms are proposed to produce physiological or pathological tremors[14-16]:

Mechanical oscillations of the extremity

This mechanism applies the approach of simple mechanical properties of any mass-spring system. The extremity (considered as a mass) coupled with joints and muscles (a spring of stiffness) will oscillate after mechanical perturbation. This resonance frequency is different for various joints (for fingers 15-20 Hz; for hands 7-9 Hz; for forearms 3-4 Hz)[17]. Cardioballistic oscillations and unsteadiness of any postural innervation cause a rhythmic modulation of the muscle force. The resonance frequency can be measured by light-weight accelerometers. Loading of the extremity reduces the resonance frequency; therefore, the technique of loading can be applied for differentiating the underlying mechanism (e.g. central tremor oscillators vs. mechanical oscillations).

Reflex activation of tremor

The oscillations of a limb are supposed to activate muscle receptors eliciting afferent volleys and evoking stretch-reflexes. For example, epinephrine and thyroid hormones can sensitize muscle spindles resulting in a more synchronized afferent volley and subsequent increase of tremor amplitude (enhanced physiological tremor).

Central oscillator

The presence of central oscillators is probably the most important factor for developing pathological tremors. Oscillations within the CNS are usually insufficient to produce tremor, since high level of synchronization is required to reach the motoneuronal pool. In the inferior olive, the electrotonic coupling through gap-junctions has been demonstrated, which may be responsible for certain pathological tremors. Other possibilities include the internal loops and abnormal coherence between various basal ganglia structures. Using intraoperative microelectrode recording (MER) techniques, for example, tremor related bursting activity could be verified in several thalamic nuclei (Vim, Voa, Vop), subthalamic nuclei and the pallidum.

Altered characteristics of feedforward and feedback loops

The abnormal functioning of the cerebellum may also produce tremor even in the absence of central oscillators[18-21]. One of the most important results of abnormal functioning of deep cerebellar nuclei is the delay of stretch-reflexes regulating stance control. For instance, the pathological functioning of the cerebellum can produce an overshot during goal-directed movements producing intention tremor.

Tremor analysis

When phenomenologically different types of tremors occur at the same time, it is difficult to separate such complex tremors solely by clinical evaluation. As the physical examination and the assessment of tremor rating scales can give only a limited portion of tremor description, the combination with electrophysiological tremor analysis might be necessary.

In this chapter some concerns about physical examination, tremor rating scales and electrophysiological analysis will be described. In the final part, I will discuss some capabilities of my tremor analyzing software.

Clinical assessment

One of the most crucial parts of the tremor description is the physical examination of tremor. The Consensus Statement of the Movement Disorders Society on Tremor gives recommendations and definitions for this purpose[2].

The physical description of a particular tremor should include the **topography** of tremor (e.g. head, chin, tongue, jaw, vocal cords, upper/lower extremity, etc.); **activation condition** of tremor (rest, postural, task-specific, non-goal-directed or goal-directed movements); and **frequency** of tremor (low: <4 Hz, medium: 4 to 7 Hz; high: >7 Hz). Besides, the examiner should also check **other neurological signs** having great impact on the differential diagnosis, such as: rigidity, cogwheel phenomenon, coactivation sign of psychogenic tremor, akinesia/bradykinesia, postural abnormalities, dystonia, cerebellar signs, pyramidal signs, neuropathic signs, gait and stance disturbances. **Froment's maneuver** ("an increase in resistance to passive movements of a limb about a joint that can be detected specifically when there is a voluntary activity of another body part")[2] may aggravate mild rigor and help the differential-diagnosis.

Rating scales

To date, neurological examination gives the most important and valuable description of tremors. Except for video accelerometry, no other electrophysiological tools can give such a detailed description of the clinical features.

However, the exact quantification and comparison of different patient's neurological status is extremely difficult even if the same neurologist performed the examinations. To improve the concordance, reliability and assessment of tremor description, various rating scales have been developed. Some of these rating scales were designed for specific etiologies or purposes (e.g. the Washington Heights-Inwood Genetic Study of Essential Tremor Rating Scale[22] could be applied in solely essential tremor to measure the efficacy

of drug treatment), while others are capable for describing several types of tremors (e.g. modified Fahn-Tolosa-Marin Tremor Rating Scale[23]).

Modified Fahn-Tolosa-Marin Tremor Rating Scale (mFTMTRS)

The original Fahn-Tolosa-Marin Tremor Rating Scale was developed for assessment of any types of tremor. It not only described the tremor characteristics, but also measured the functional disability and impact of tremor in the terms of the patients' ability to work and carry out several daily activities. The revised version of the scale[23] incorporated some items used in the tremor scale developed by the Tremor Investigation Group and currently became a widely applied technique in drug trials and research activities[24-28].

The scale is divided into three parts. Part A (with a maximum score of 80) quantifies tremor at rest, during posture, and kinetic maneuvers for nine parts of the body. Contrary to other former tremor rating scales[29], mFTMTRS provides definitions for the use of the 5-point severity scale from zero (none) to four (severe), which is supposed to improve concordance among clinicians. Part B (with a maximum score of 36) rates action tremor of the upper limbs, particularly during writing, drawing spirals and pouring liquids. In part C, the patient evaluates the impact of tremor on his or her functional disability (speaking, feeding, drinking, hygienic activities, dressing, writing, and working) with a maximum score of 28. The total score obtained by adding the three parts of the mFTMTRS is 144. Finally, the mFTMTRS includes one separate item dealing with global assessment of tremor related disability, rated by both patient and examiner on a 5 point scale.

The advantage of the use of mFTMTRS is that the postoperative outcome of essential tremor (ET) and idiopathic Parkinson's disease (PD) becomes comparable regarding the tremor severity.

Interestingly, the **manual performance** can also be estimated by measuring the time required writing a sentence or drawing a spiral. That was the reason why not only FTMTRS, but also manual performance time values were obtained during in our tremor-related investigations[30, 31].

Unified Parkinson's Disease Rating Scale

The Unified Parkinson's Disease Rating Scale (UPDRS) was originally developed in the 1980s[32] and has become the most widely used clinical rating scale for PD[33].

UPDRS is a single scale with four subscales for use in both research and clinical care settings. Each of the four parts can be summed to render a total or analyzed separately. The first section tests the motivation, mood and mentation of the patient with the maximum score of 16. The second part quantifies the activities of daily living in both 'on' and 'off' states. Among others speech, salivation, swallowing, hand writing, eating, hygienic activities and walking is described in details (52 points maximum). The third

section, referred to as the “motor examination”, evaluates the most important Parkinsonian symptoms: speech disturbances, facial expression, tremor, rigor, bradykinesia, rapid alternating movements, posture, postural stability and gait disturbances. The motor examination section can be applied for measuring disease progression and evaluating the efficacy of both drug- and surgical therapies with the maximum score of 108 points. The fourth section is suitable for describing the complications and side-effects of the medical therapy (e.g. dyskinesia, fluctuation, dystonia and anorexia).

Although UPDRS is a gold-standard for evaluating drug-efficacy, it is not the appropriate tool for capturing the changes of Parkinsonian tremor. For instance, the UPDRS does not describe precisely the postural and kinetic tremor of the patients. Therefore, in case of Parkinson’s disease I have applied both FTMTRS and UPDRS to detect the postsurgical improvements in tremor and other Parkinsonian symptoms, respectively.

Electrophysiological tools

Electrophysiological measurements have several advantages over pure clinical examinations. The two most important points to be discussed are the good time resolution and the ability to quantify those characteristics, which are hidden to the naked eyes. Tremor is fluctuating by the minute; almost invisible tremor segments may abrupt serious, disabling tremor segments. Using tremor rating scales we can describe the amplitude intuitively and categorize tremor based on the given descriptions, but the ever-changing nature of tremor must be either videotaped or electrophysiologically recorded for further analyses. Besides capturing the dynamics, the electrophysiological tools are also superb in quantifying various tremor characteristics (e.g. frequency, intensity, asymmetry, entropy, etc.).

For the purpose of tremor analysis, I have simultaneously applied accelerometry, surface electromyography (sEMG) and video recording. Beside the technique of recording, I will describe the major steps of post-processing and the most important electrophysiological parameters in details.

Accelerometry

Accelerometry, a type of actigraphy, is an electrophysiological tool to analyze the movements of the examined limb by detecting acceleration. The method can be assessed for several purposes:

- to quantify tremor characteristics (e.g. amplitude, frequency)[34, 35],

- to help clinical differential-diagnosis[36-41] (e.g. physiological vs. pathological tremor, essential vs. Parkinsonian tremor, pathological vs. psychogenic tremor),
- to objectively measure the efficacy of various drug treatments[42-44], and
- to objectively measure the efficacy of various neurosurgical treatments[45].

The sensors can generally detect the acceleration in one (uniaxial), two (biaxial) or three (triaxial) planes. During measurements, the sensors are usually attached firmly to the dorsal surface of third metacarpus. The triaxial accelerometry we use is the combination of ADXL 105 and ADXL 320 sensors (Analog Devices, Norwood, MA), which are capable of detecting acceleration in the range of ±5g on both hands simultaneously with the resolution of 2 milli-g^2 (1g equals with the acceleration of the Earth's gravity, 9.807 m/s^2). The weight of this equipment is less than 15 gram, which practically does not interfere with the tremor **(Figure 1)**.

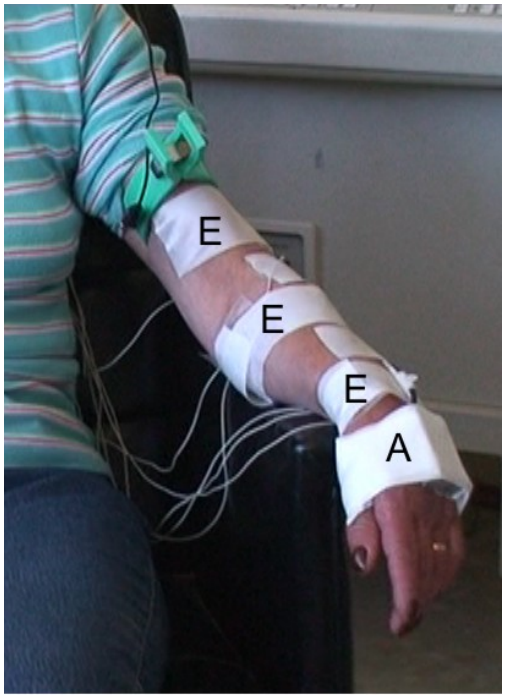

Figure 1. Typical setting of tremor recording. *During rest tremor evaluations, the wrists are supported and the hands can dangle freely. Light-weight accelerometers are taped over the 3rd metacarpus (A), and sEMG electrodes are attached over the belly of forearm muscles (E).*

All tremor assessments were carried out using the same procedure:

- **Rest tremor** of both hands was recorded for at least 5-15 minutes in each case. The patients sat in a comfortable chair and were asked to relax their hands during the measurements. The hands were supported at the level of wrists; therefore, they were able to dangle freely.
- **Postural tremor** could be recorded in two different ways: the whole arms or only the hands maintained against gravity. If the whole arms were elevated, the amplitude of tremor was usually higher (good for video recordings), but in this way

the muscles of the upper arm were also participating in the tremor genesis. If we were interested in the hand tremor only, the wrists were supported by the arm of the chair and the patient had to maintain this position horizontally against the gravity (e.g. with using a visual target).

- **Kinetic tremor** of each side was assessed in two conditions: performing non-goal-directed and goal-directed movements. During non-goal-directed movements, the patient flexed and extended slowly his or her elbow in a horizontal plane. To record the intention tremor, we asked the patient to carry out finger-to-nose maneuvers with the eyes closed. While one of the hands was performing these kinetic maneuvers, the other was maintaining the resting position.
- **Loading** is an important technique to distinguish tremors generated by central and mechanical reflex mechanisms. During the loading, the patient maintained the same position as during postural tremor recording, but either a 500 g or a 1000 g load was attached firmly to the dorsal surface of the hand.

The signal of the accelerometer was digitized by Power 1401 ADC (Cambridge Electronic Design Ltd, Cambridge, UK). The optimal gain was set by the tremor recording software automatically.

Surface electromyography, sEMG

The use of surface EMG is an essential tool for investigating physiological and pathological tremors. The sole detection of acceleration (or velocity or displacement) of the limb is usually insufficient to describe the mechanism in tremor genesis. A good example is the differentiation of Parkinsonian tremor from essential tremor: Applying only accelerometry, the two etiologies cannot be distinguished from each other in approximately 30-50% of the cases. However, if both accelerometric and sEMG signals are analyzed, the neurophysiological criteria for ET, for example, show a sensitivity of 97.7%, a specificity of 82.7%, a positive predictive value of 95.1% and a negative predictive value of 91.1%[36].

The most important applications of sEMG are the following:

- to test the presence or absence of tremor-related bursting,
- to identify the muscles involved in tremor,
- to determine activation timing, and
- to estimate the force produced by the muscle.

In my studies, I always combined accelerometry with surface electromyography whenever it was possible. Both hands were examined simultaneously using silver/silver-chloride electrodes. These electrodes were firmly attached in a bipolar mode to the belly

of the flexor and extensor forearm muscles. In addition, the sEMG activity of biceps and triceps muscles could also be recorded when it was required **(Figure 1** and **Figure 2)**.

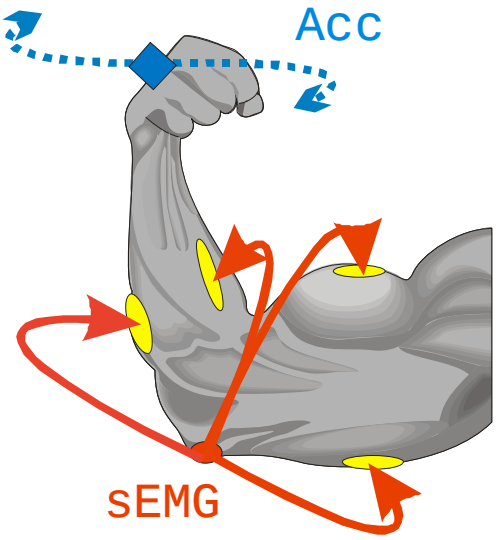

Figure 2. If a specific situation required it, uni- or bipolar sEMG could be also used. *In the cases of unipolar sEMG, the common reference electrode was placed over the olecranon (Dotted line demonstrates the detection of acceleration and the solid lines represent the recording of sEMG signals.*

The reference electrode (at times called ground electrode) was placed as far away as possible on an electronically neutral tissue (e.g. a bony prominence). After all electrodes were taped to the skin, electrically conductive gel was injected into the space between the metal surface and the skin through the center hole of the electrodes. In these examinations a 16 channel electroencephalograph (EEG16, Medicor, Hungary) served as a differential-amplifier; its analog output was digitized by a Power1401 AD converter. The gain of each channel was either manually set or automatically chosen by the recording software to achieve optimal digitization.

The technique of digitization

Both accelerometry and surface electromyography generates analog signals. Analog signals are voltage signals that are analogous to the physical signal they represent. The amplitude of these signals typically varies continuously throughout their range. Contrary, digital signals use sequences of numbers to describe the physical signal. Therefore, digital information is different from its continuous counterpart in two important respects: it is sampled, and it is quantized.

The digitization process generates a sequence of numbers, each representing the amplitude of the analog signal at a specific point in time. The whole process can be broken into two components: *sampling* and *quantization*[46] **(Figure 3).** Both of these processes restrict how much information a digital signal can contain.

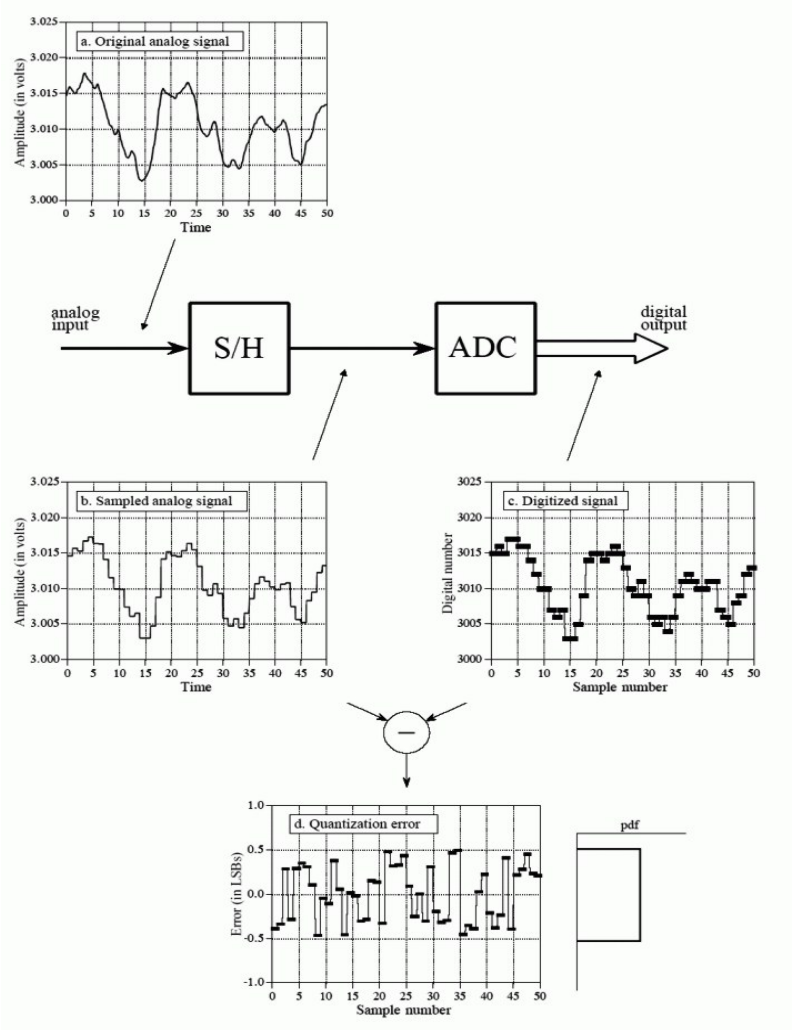

Figure 3. Digitization of an analog signal. *The conversion is broken down into two stages to allow the effects of sampling (S/H) to be separated from the effects of quantization (ADC). (Modified from The Scientist and Engineer's Guide to Digital Signal Processing by Steven W. Smith[46])*

Sampling is determined mainly by the process of sample-and-hold (S/H), which is required to keep the voltage constant while the analog-to-digital conversion (ADC) is taking place. As shown by the difference between (a) and (b) on **Figure 3**, the output of the sample-and-hold is allowed to change only at periodic intervals. The length of these intervals is determined by the sampling frequency, which is typically expressed in Hertz.

During ***quantization,*** the amplitude (voltage) values are converted to integer numbers. This introduces an error, since the resolution of the amplitude is determined by the characteristics of the AD converter (e.g. 12- or 16-bit converter). For example, both 3.14000 volts and 3.14001 volts can be converted into the same digital number if the difference between these values is below the resolution of the converter.

To minimize the error derived from the digitization procedure, we must comply with the sampling theorem. The sampling theorem (or the Nyquist theorem) indicates that a

continuous signal can be properly sampled, only if it does not contain frequency components above one-half of the sampling rate. In other word, a sinusoid signal can only be correctly recreated if it is sampled at no less than twice of its frequency. Violating the Nyquist theorem leads to an incorrect reconstruction of the signal typically referred to as aliasing. For example, to correctly record a 0-10 Hz signal we need to use at least 20 Hz sampling rate. However, the noise between 10-20 Hz still could produce an aliasing effect on the acquired data. Therefore, an analogue filter has to be applied before digitization, which is called *anti-aliasing filter* **(Figure 4)**.

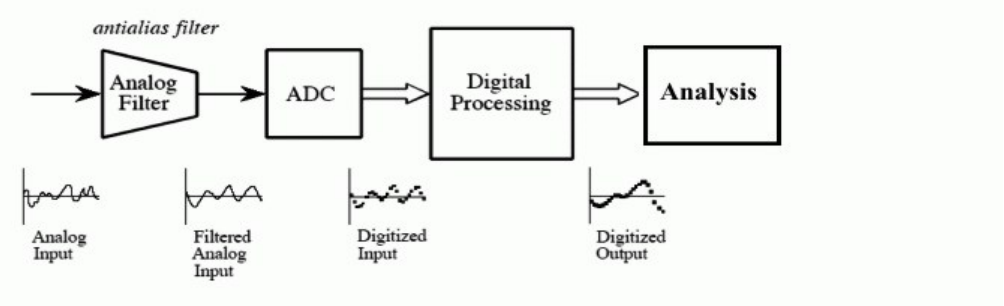

Figure 4. The flowchart of digitization process. *(Modified from The Scientist and Engineer's Guide to Digital Signal Processing by Steven W. Smith[46])*

Based on these theoretical considerations, in the present experiments accelerometric, electromyographic and electroencephalographic data were filtered with a 500 Hz low pass anti-aliasing filter and subsequently digitized with 1000 Hz sampling rate by a 16-bit Power1401 AD converter (Cambridge Electronic Design Ltd, Cambridge, UK). This AD converter was capable of sampling simultaneously 32 waveform channels with up to 625 kHz sampling rate. The built-in gain between 1-1000x range could be controlled by the recording software to achieve the optimal signal-to-noise ratio.

SEVAS, **S**imultaneous **E**lectrophysiological, **V**ideo recording and **A**nalyzing **S**oftware

One of the great advantages of digital data capturing is that the analysis can be performed at any time later. Based on the type of the data and the aim of the analysis, the "raw" data has to be modified to increase the signal-to-noise ratio by using artifact removal, DC-removal and digital filtering techniques (post-processing). The actual analysis of the recordings can only be performed subsequently.

Since post-processing can be performed more or less in a similar way on each recording, using Spike2 script language (version 5 and 6, Cambridge Electronic Design Ltd., Cambridge, UK) I developed a software for recording, post-processing and performing semi-automated analysis. This highly configurable program is not only able to manage the patient and exam information, synchronize the accelerometric, sEMG, EEG and video signals, select the optimal gain level during recording, perform individualized

artifact removal, apply customized filtering and carry out several calculations, but also writes the results automatically into a database. Since each exam is labeled by an alphanumerical ID during the recording, the offline analyses can be performed in a blind way since the examiner knows neither the identity of the patient nor the nature of the recording (e.g. preoperative, postoperative or control) **(Figure 5)**.

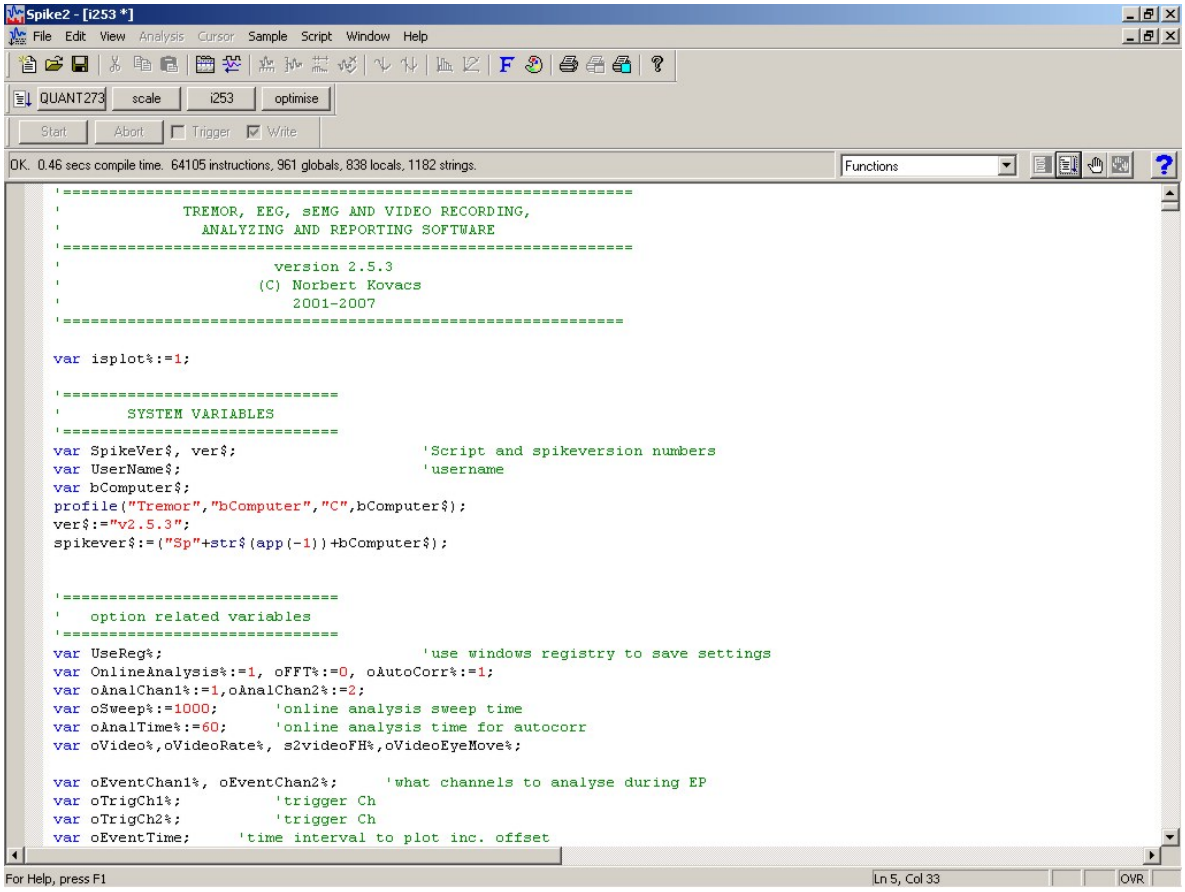

Figure 5. A sample from the source code of my electrophysiological recording and analyzing software. *The program is written in Spike2 script language and the actual version (v2.53) contains 64105 instructions.*

Post-processing

During post-processing, the “raw” data is cleared from technical artifacts and noise, which makes it suitable for further qualitative and quantitative analyses. Post-processing may include the following steps:

- Removing artifacts
- Removing DC-offset
- Filtering of the signal
- Performing various mathematical techniques, such as waveform correlation and fast Fourier transform, which are suitable for quantitative analysis (e.g. frequency, intensity, asymmetry index, and irregularity)
- Saving the results automatically into a spreadsheet.

My program is capable of changing various post-processing settings according to the study design **(Figure 6)**.

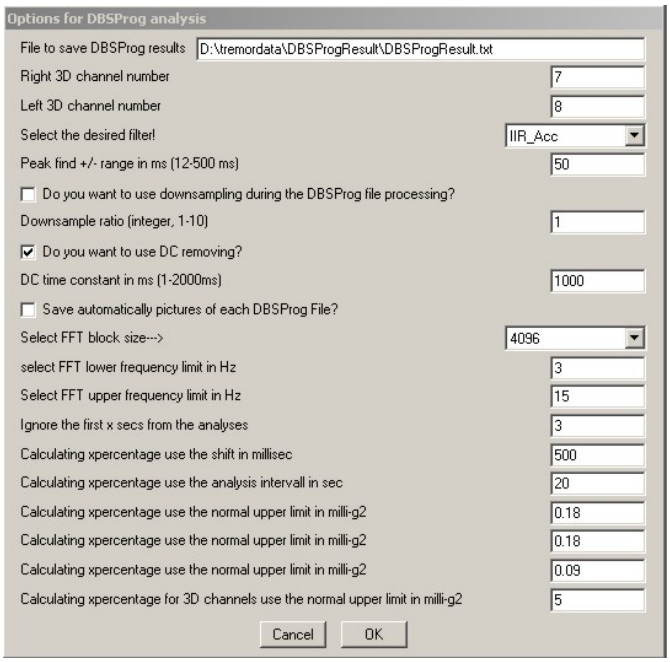

Figure 6. Using Spike2 scripting language, I have developed a highly individualized post-processing software module. *In this example, among others, the examiner can change the filter selection, the settings of automated peak-detection, Fourier Transform block-size and decide on the use of down-sampling and DC-removing techniques.*

Semi-automated artifact removal

One of the major drawbacks of electrophysiological recordings is the presence of various artifacts. The best known example is the eye- and electrode-movement artifacts detectable on the electroencephalograms. In order to carry out reliable and accurate calculations on the recordings, these artifacts have to be eliminated first.

Based on a sample code provided by the Cambridge Electronic Design Ltd (Cambridge, UK), I have implemented a semi-automated artifact removal technique. During this process, the script browses through every channel of each recording and whenever identifies a suspicious segment, it gives a warning message. By surveying, the examiner makes the final settlement whether to accept the segment in question as an artifact or not. If the situation is ambiguous, the examiner can also check the simultaneous video-recording before making this decision. In addition to this, the first 3 seconds of each recording is always considered as an artifact due to the limitations of digital filtering. Obviously, all sections marked as artifact are practically excluded from the further analyses.

DC offset removing

DC offset is an offsetting of a signal from zero. The term originated in electronics, where it refers to a direct current voltage, but the concept has been extended to any representations of waveform data. DC offset is the mean amplitude of the waveform; if the mean amplitude is zero, there is no DC offset[46]. DC offset is usually undesirable and may also cause artifacts depending on what is being done with the signal. To avoid the problem of DC offset, I have applied a special DC-removal script as the part of post-processing, where the time constant was usually set between 1000 and 3000 ms.

Filtering

Filtering can be applied to remove unwanted frequency components (e.g. contaminating noise) from waveforms. In electrophysiology, both hardware-based (analog) and software-based (digital) filters are available. Digital filters, in comparison, are vastly superior in the level of performance that can be achieved, since they can have thousands of times better performance than the analog filters[46]. Therefore, during data acquisition, I avoided any unnecessary hardware filtering and left this task over to the digital filters. This approach enabled me to develop different filtering methods for various types of data (e.g. accelerometric, EEG and sEMG signals).

The ideal digital filter

Each digital filter must fulfill certain time and frequency domain criteria. The most important **time domain** property is the transition speed. To distinguish events in a signal, the duration of the step response must be shorter than the spacing of the events. This dictates that the step response should be as fast as possible.

Figure 7 shows the four basic **frequency domain** responses. The purpose of these filters is to allow some frequencies to pass unaltered, while completely blocking other frequencies.

The ***passband*** refers to those frequencies that are passed, while the ***stopband*** contains those frequencies that are blocked. The ***transition band*** is between. A ***fast roll-off*** means that the transition band is very narrow. The division between the passband and transition band is called the ***cutoff frequency*** (defined as the point where the amplitude is reduced to 0.707 or in other words the attenuation is -3dB).

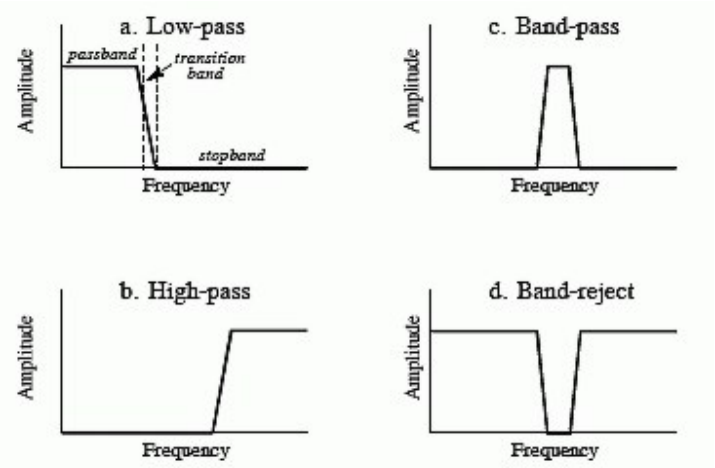

Figure 7. The four basic filter types based on the frequency domain properties (low-pass, high-pass, band-pass and band-reject) *(Modified from The Scientist and Engineer's Guide to Digital Signal Processing by Steven W. Smith[46])*

During filter-designing, one must carefully select the filter parameters to achieve fast roll-off with good stopband attenuation without ripples in the passband **(Figure 8)**.

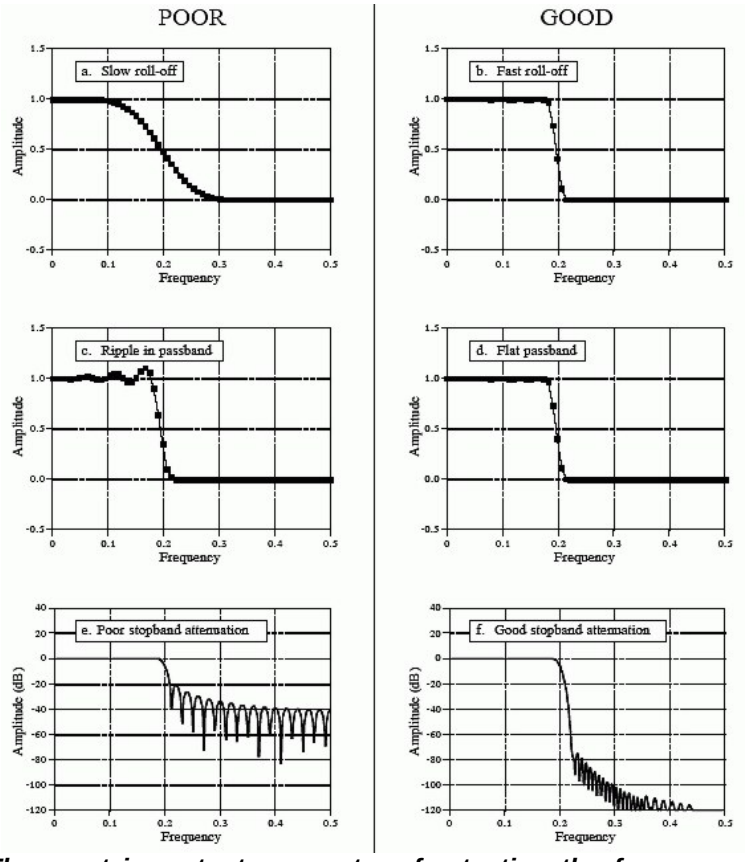

Figure 8. The most important parameters for testing the frequency domain performance. *Three important parameters must be considered: (1) roll-off sharpness shown in parts a and b, (2) passband ripple presented in parts c and d, and (3) stopband attenuation demonstrated in parts e and f. (Modified from The Scientist and Engineer's Guide to Digital Signal Processing by Steven W. Smith[46])*

Based on the underlying filtering technique, we can distinguish Infinite Impulse Response (IIR) and Finite Impulse Response (FIR) filters. They have several advantages and disadvantages; therefore, different types of filters have to be designed for different tasks.

Infinite impulse response (IIR) filters

Applying IIR filters is an efficient way of achieving a long impulse response, without having to perform a long convolution. They execute very rapidly, but have less performance and flexibility than other digital filters. Their impulse responses are composed of decaying exponentials, which are similar to analogue filters. Digital IIR filters are designed to map standard Butterworth, Bessel, Chebyshev filters and resonators into their digital forms.

IIR filters have advantages:

- They can generate much steeper edges and narrower notches than FIR filters.
- IIR filters are causal; they do not use future data to calculate the output, so there is no pre-ringing due to transients.

They also have disadvantages:

- IIR filters are prone to stability problems particularly as the filter order increases or when a filter feature becomes very narrow compared to the sample rate. However, the careful design of the filter can prevent this type of instability in most cases.
- IIR filters impose a group delay on the data that varies with frequency. This means that they do not preserve the shape of a waveform, in particular, the positions of peaks and troughs can change depending on the filter settings. This phenomenon can introduce several inaccuracies during data analysis, which can be prevented by applying similar types of filters on each waveform data (e.g. IIR filters for both accelerometric and sEMG recordings).
- The output of an IIR filter may take a long time to settle down from the discontinuity at the start (e.g. transition from no data to the supplied data). I overrode this problem by excluding the first 3 seconds of each recording from further analyses.

Finite impulse response (FIR) filters

The moving average (or finite impulse) filter is the most common filter, mainly because it is the easiest digital filter to understand and use. The FIR filter is optimal for common tasks, for example, reducing random noise while retaining a sharp step response. However, the FIR filters are the worst filter for frequency domain encoded signals, with little ability to separate one band of frequencies from another.

FIR filters have advantages:

- They are unconditionally stable as they do not feedback the output to the input.
- There is no phase delay through the filter, so peaks and troughs do not move when data is filtered.

They also have disadvantages:

- They are poor at generating very narrow notches or narrow band pass filters.
- The narrowest frequency band or band gap is limited by the number of coefficients.
- FIR filters are not causal; they use future as well as past data to generate each output point. Therefore, a transient in the input causes effects in the output even before the occurrence of the transient event (pre-ringing).

Based on technical reviews[47] and utilizing my own experiences, I implemented different digital filters for the accelerometric, EEG and sEMG recordings to achieve maximal noise and artifact removal with minimal signal distorsion. A detailed description of the applied filters is shown in **Table 1**, while the sample characteristics of a band-pass filter can be found on **Figure 9**.

Data	***Filter-type***	***Model***	***Num. of constants***	***Low edge***	***High edge***	***Order***
Accelerometric	IIR band-pass	Butterworth	---	0.7 Hz	35 Hz	4th
sEMG	IIR band-pass	Butterworth	---	0.7 Hz	250 Hz	4th
EEG	IIR high-pass and FIR low-pass	Butterworth Hamming	--- 229	--- 35 Hz	0.35Hz ---	4th ---

Table 1. Detailed descriptions of the applied digital filters. *During the post-processing of EEG signals, first a Butterworth IIR high-pass filter was applied and subsequently a low-pass FIR filter.*

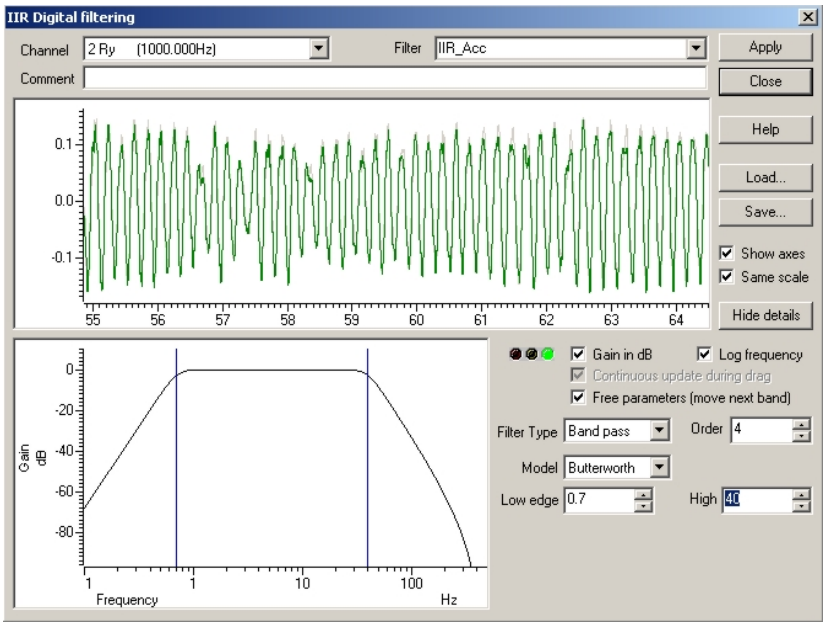

Figure 9. Digital filter designing procedure. *To maximize signal-to-noise ratio, digital filters have to be applied on the accelerometric, EEG and sEMG signals. For an example, the most important parameters and the characteristics of a band-pass IIR filter are presented.*

Waveform correlation

In the statistical toolkits, the correlation coefficients measures how variables or rank orders are related. Correlation can range in value from –1 (a perfect negative relationship) to +1 (a perfect positive relationship), while the value of 0 indicates no linear relationship.

Analogously, the ***waveform correlation*** measures the similarity of two waveform recordings in the time domain. In the analysis of tremor signals, the waveform correlation is calculated usually in the +/- 1 second time-range.

The correlation is calculated by multiplying the two waveforms together, point by point, and summing the products. The sum is normalized to allow for waveform amplitudes and the number of points, which produces one result. Subsequently, the reference waveform moves one point to the right and the process is repeated to produce the next result. This process is repeated for all the data points in the selected time-range. The waveform correlations range between 1.0, meaning the waves are identical (except for amplitude) through 0 (un-correlated) to -1.0, meaning identical but inverted. Finally, all calculated results are plotted on a graph, the so-called waveform correlation spectrum **(Figure 10)**.

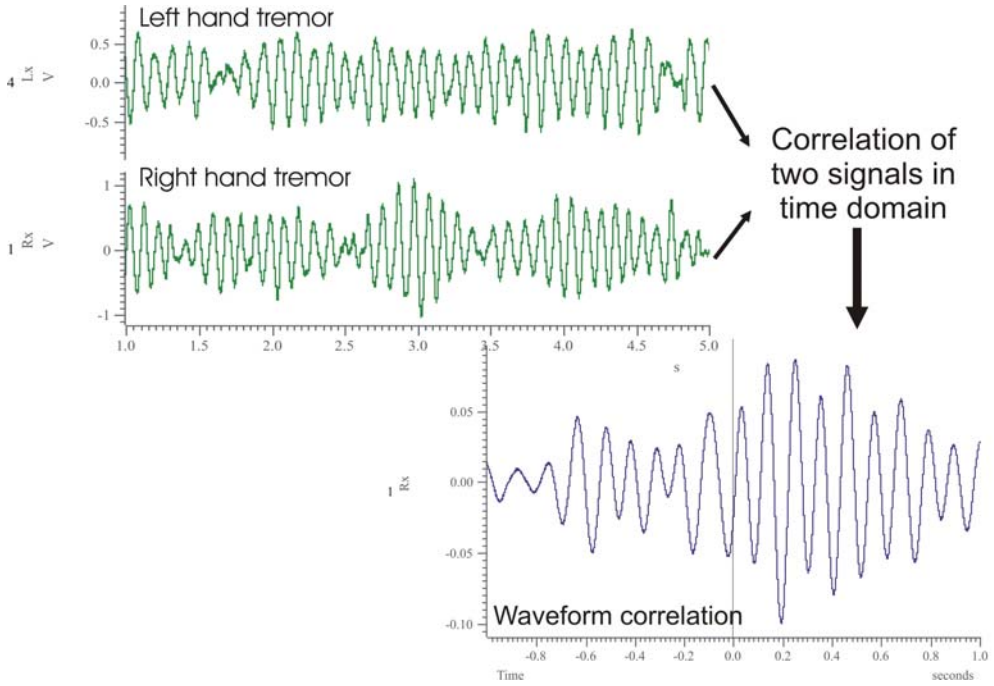

Figure 10. Calculation of a waveform correlation. *To test the hypothesis that the left and the right rest tremor signals are similar, we can calculate the correlation in the time-domain (+/- 1 second). The low correlation values (0.09 maximum and -0.10 minimum) suggest that the right and left tremors are probably not analogous in the presented case.*

Autocorrelation

If an electrophysiological recording is correlated to itself by applying the waveform correlation method, the ***autocorrelation*** is given as the result. The primary use of autocorrelation is to unhide the periodicity of a signal. Assuming that the tremor consists

of more or less regular oscillations, the autocorrelation will produce high values at the period-length of tremor signal.

At zero time shift, the autocorrelation always gives the value of 1, since two identical curves are compared; therefore, their correlation is always the maximum. Theoretically the second highest peak on the autocorrelation corresponds to the period-length of the signal. Consequently, the inverse value of this period-length will give the frequency of tremor **(Figure 11** and **Figure 13)**.

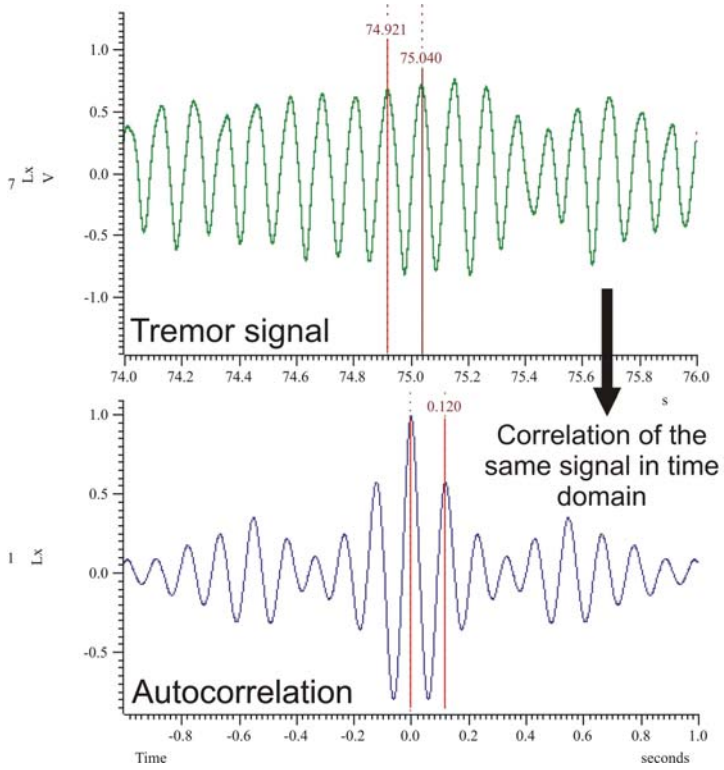

Figure 11. Autocorrelation. *If a waveform data is correlated to itself, the autocorrelation is calculated. Autocorrelation is suitable to analyze the main frequency of a signal, since the second highest peak refers to the period-length of the signal.*

Power-spectrum

Fast Fourier Transform (FFT) is a tool to convert the waveform data into a power spectrum. Mathematically, the FFT is a device that transforms a block of data between a waveform and an equivalent representation as a set of cosine waves. The FFT that I used for the calculations limited the size of the data blocks to be transformed to 4096 or 8192.

The result diagram spans a frequency range from 0 to half the sampling rate of the waveform channel. The width of each bin is given by the waveform channel sampling rate divided by the FFT block size. (As 1000 Hz sampling frequency was used during my examinations, the resolution of frequency was 1000 Hz/8192, approximately 0.12 Hz). The resolution in frequency improves as you increase the block size, however, the resolution in time decreases simultaneously[46]. The result of the analysis is scaled to root mean

square (RMS) power, so it can be converted to energy by multiplying by the time over which the transform was done.

To sum it up, the power-spectrum is suitable for calculating the intensity and the frequency of a signal in certain cases **(Figure 12)**.

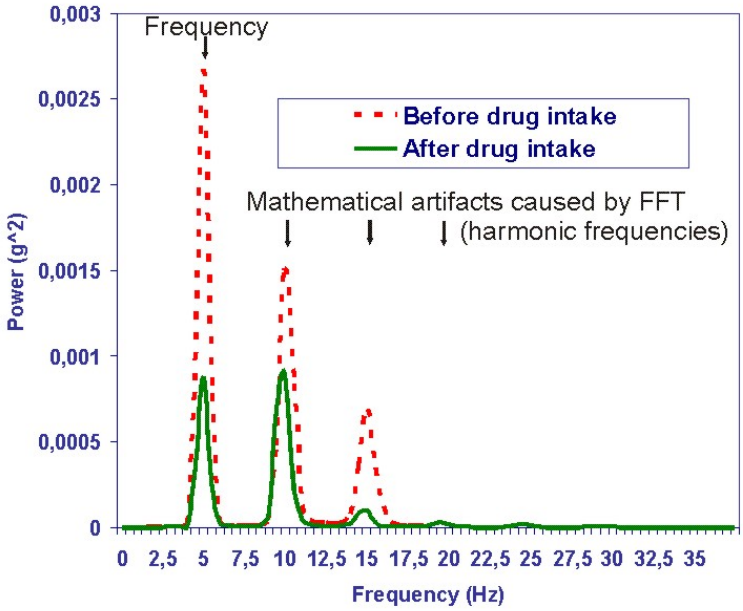

Figure 12. Power-spectrum. *The power-spectra of the postural tremor before (dotted line) and after drug intake (solid line) are presented in the case of an essential tremor patient. Power spectrum can be used for calculating both intensity and frequency. The tremor intensity is measured as the area under the curve and the frequency is usually considered as the highest peak on the power-spectrum. N.B.: Fast Fourier Transform can produce mathematical artifacts at the harmonic frequencies (marked with arrows), which may have influence on frequency calculation. Acceleration is given in gravity, 1g equals with 9.807 m/s^2.*

Analysis of accelerometric recordings

1. Frequency

Frequency is still the most useful electrophysiological property in the differential-diagnosis of pathological and physiological tremor types[48]. During the frequency calculation, we assume that the tremor is a more or less regular phenomenon, which is built by regular sinusoid components.

Basically, two different approaches can be applied to determine the tremor frequency: one is based on (1) power-spectrum and the other on (2) autocorrelation.

Power-spectrum method

In most studies, the frequency was defined as the highest peak on the power-spectrum[36, 49-51]. Unfortunately, the Fourier transform sometimes induces mathematical artifacts:

- FFT usually produces false high intensity values at harmonic frequencies. For example, if the sampled data were a perfect sine wave with 5 Hz, we would expect

only one peak on the power-spectrum at 5 Hz. However, the mathematical procedure would create high values also at the harmonic frequencies (e.g. 2x5= 10 Hz, 3x5=15 Hz), as well **(Figure 12)**. Moreover, we found some cases where the harmonic frequencies had higher intensity values than the real frequency **(Figure 13, part C)**; therefore, FFT should be applied cautiously for frequency analysis.

- The mathematics behind the FFT assumes that the input waveform repeats cyclically. In most recordings this is far from the case; if the blocks were spliced end to end there would be sharp discontinuities between the end of one block and the start of the next. Unless something is done to prevent it, these sharp discontinuities could cause additional frequency components in the result.
- The accuracy of frequency determination also depends on the applied FFT block size. Higher the block size gives a better frequency resolution, however, at the expense of worse time resolution.

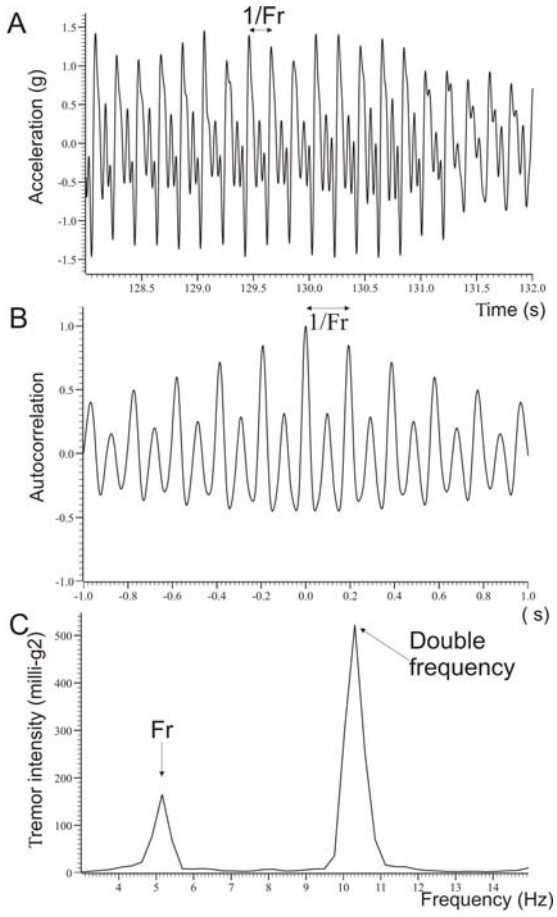

Figure 13. False frequency determination by power-spectrum. *Frequency of tremor was calculated by a semi-automated script comparing the accelerometric recording (A) to its autocorrelation (B) and power-spectrum (C). Acceleration is given in gravity (1g = 9.807 m/s^2). Time intervals between peaks of both autocorrelation and waveform recordings are the period-lengths of the tremor marked with "1/Fr". (The inverse value of period-length gives the frequency of tremor.) On the power-spectrum, the frequency of tremor and its harmonic double frequency are labeled. Note that the highest peak in the power-spectrum does not necessarily respect the real frequency of rest tremor.*

Autocorrelation method

Recent studies apply autocorrelation instead of power-spectrum to determine tremor frequency [52-54]. The autocorrelation function measures the similarity of a waveform to itself in time domain. Assuming that the tremor is a quasi regular oscillatory movement, high correlation values could be expected at the period-length of the tremor. Therefore, the second highest peak on the autocorrelation spectrum respects the period-length of the tremor and its inverse value gives the frequency in Hz **(Figure 13, part B)**.

However, one of the most important disadvantages of the autocorrelation has to be also mentioned. If we calculate correlations over long sections of data, the calculations can take some considerable time (e.g. in the case of a recording lasting for 30 minutes containing 1000 data points in every second, the process can take several seconds).

"Compromise"-method

To overcome the limitations of the described methods, I developed the tremor analysis module of the program in a way combining both methods. During the evaluation, both autocorrelation- and power-spectra were drawn and the semi-automated script calculated the period-length from the autocorrelation-spectrum and the frequency from the power-spectrum **(Figure 14)**. If both methods gave the same outcome, the result could be accepted automatically. In case of discrepancy, the frequency-analysis of the video recording made by the examiner could settle the question.

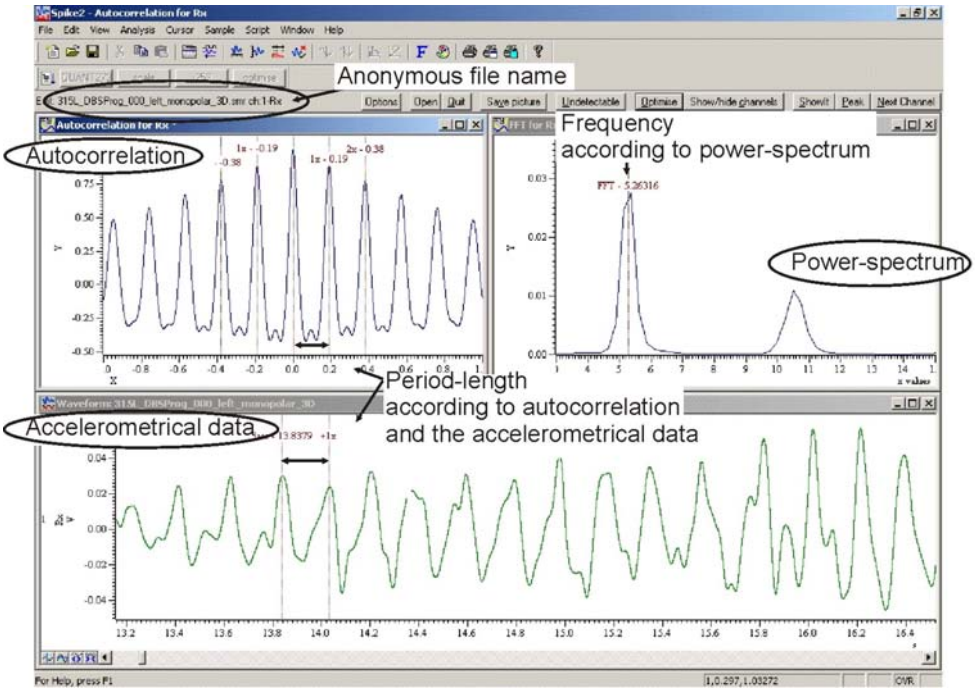

Figure 14. Frequency analysis using both autocorrelation and fast Fourier transform (power-spectrum). *On the autocorrelation curve, the interval between the highest and the second highest peaks equals with the period-length of tremor oscillation, while the highest peak on the power spectrum usually demonstrates the frequency. In most cases, both methods give the same outcome. (Distances marked with arrows represent the period-length).*

In more than 98% of the cases, both autocorrelation and FFT analysis came to the same frequency value. In my experience, in the cases of discrepancy, always the autocorrelation gave the good frequency value according to the video-analyses.

2. Intensity (total power, TP)

Fast Fourier Transform quantitatively describes the components of waveform data in the frequency domain and creates a plotting called power-spectrum, which can be converted to energy (i.e. intensity). As the power-spectrum is drawn as root mean square (RMS), total power (TP) can be calculated as the area under the curve in the range of 3-15 Hz. The total power straightforwardly correlates with the amplitude of the tremor; therefore, the amplitude of tremor oscillation can be simply calculated using the TP value.

3. Asymmetry-index (AI)

Clinically, the Parkinsonian rest tremor is usually asymmetric having higher intensity on the more affected side. This property can be quantified by the asymmetry index[55]:

$$\mathrm{AI} = \frac{Abs(right - left)}{\frac{(right + left)}{2}} \times 100,$$

where Abs means the absolute value, and left and right mean the appropriate total power values. Consequently, a higher AI value indicates a clinically higher asymmetry.

4. Irregularity

Frequency, intensity and asymmetry-index treat the tremor as a linear phenomenon. However, tremor is demonstrated to satisfy the definition of nonlinear systems[56-59]. ***Nonlinear systems*** represent systems whose behavior is not expressible as a sum of the behaviors of its descriptors. Since nonlinear systems are not equal to the sum of their parts, they are often difficult (or impossible) to model, and their behavior with respect to a given variable (e.g. time) is extremely difficult to predict[60]. When modeling non-linear systems, therefore, it is common to approximate them as linear, where possible[61].

Entropy measurements can utilize the nonlinear nature of tremors to calculate regularity and complexity. In my research, two entirely different entropy tools were applied: a classical entropy approach (approximate entropy, ApEn) and a more recent and sophisticated one (multiscale entropy, MSE).

Approximate entropy (ApEn)

Traditional entropy measurements, such as ApEn, quantify only the regularity (predictability) of time series on a single scale[62]. ApEn reflects the likelihood that “similar” patterns of observations will not be followed by additional “similar” observations. A time

series containing many repetitive patterns has a relatively small ApEn; a less predictable data have higher ApEn values[63]. However, ApEn has a significant limitation: There is no straightforward correspondence, between regularity and complexity[62], therefore, the ApEn value describes only predictability and not the complexity of the signal.

Multiscale entropy (MSE)

MSE is a refinement of approximate entropy, which is capable of measuring the complexity of physiological data sets. Up to this time, there is no consensus definition of complexity. Intuitively, complexity is associated with "meaningful structural richness" incorporating correlations over multiple spatio-temporal scales[64]. During the MSE process, entropy is calculated at different scale factors and plotted as a function of the scale factor. The primary aim of MSE is to unhide such tendencies and phenomena that cannot be captured by using either linear methods or traditional entropy measurements.

Assuming that pathological tremors generated by highly synchronized neuronal networks, we can expect it being more regular, predictable and less complex than the physiological tremor originating from several distinct compartments (e.g. mechanical-reflex components and cardioballistic movements). To test this hypothesis in the respect of neurosurgical treatments, I have implemented the freely downloadable and usable approximate entropy and MSE calculation methods in the routine tremor analysis. (MSE source code is still available at http://www.physionet.org/physiotools/mse/mse.c, however, the code of ApEn has been removed recently from the server in deference to the wishes of SM Pincus, the author[65]) **(Figure 15)**.

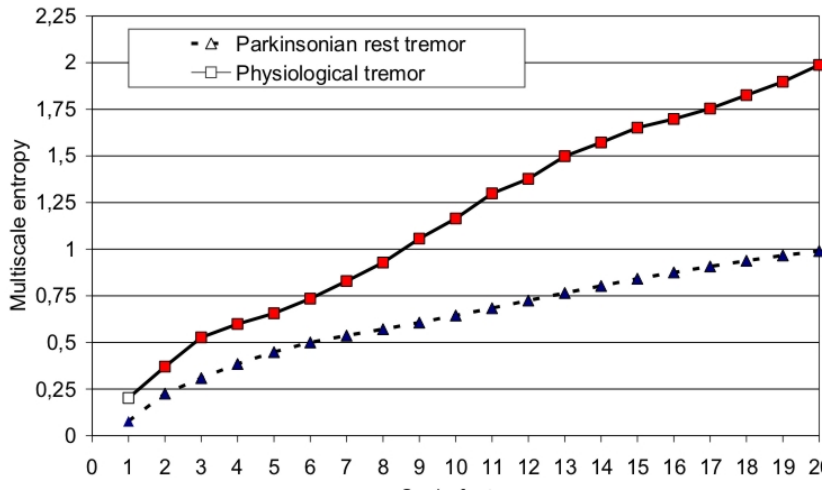

Figure 15. Multiscale entropy (MSE) analysis of physiological and Parkinsonian rest tremor. *The higher MSE values mean either higher irregularity (at low scale levels, e.g. 1) or higher complexity (at high scale levels, e.g. 20). Traditional entropy methods capture the low scale properties of the signal, which may show less prominent differences than MSE can demonstrate at high scale factors (e.g. MSE can be applied for revealing the differences between the Parkinsonian and physiological rest tremors. The significance level at the scale of 1 was p<0.05, which improved at the scale of 20, p<0.001). During MSE calculations, the suggested parameters were used (m=2, r=0.2xSD).*

5. Number of peaks on power-spectra

Morphology of power-spectra can be quantified by the number of independent peaks in the range of 3-15 Hz, where a peak is defined as an increase of at least 3 frequency bins from the surrounding bins on either side.

Obviously the comparison of the number of peaks between different cases requires the use of standard procedure: 1000 Hz sampling rate, identical DC-removing and filtering methods, constant block-size during the fast Fourier transform (8192), and the same windowing method (hamming).

Analysis of surface electromyography

The analysis of surface EMG signals involves also several qualitative and quantitative parameters similarly to that of accelerometric recordings.

1. Presence of tremor related burst activity

One of the most important qualitative characteristics of surface EMG is the presence or absence of tremor-related burst activity **(Figure 16)**.

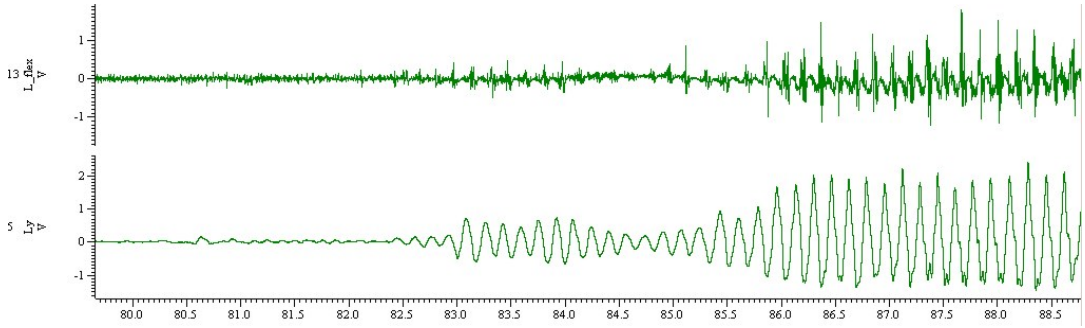

Figure 16. The appearance of tremor-related burst activity on sEMG. *The thalamic (Vim) deep brain stimulation was turned off at the time of 80.5 seconds. Tremor-related burst activity (upper signal) and consequent high intensity tremor (bottom signal) shortly developed afterwards.*

2. Burst duration

In some cases, the duration of individual bursts can be important. A semi-automated script can calculate the length of each burst and subsequently give the mean and standard deviation values.

3. Frequency

Fast Fourier Transform (power-spectrum) can be also calculated for each surface EMG channels. It is a useful tool if we are interested in the frequency content of sEMG signals (e.g. calculating fatigue index of a certain muscle, because during sustained contractions the median frequency shifts to lower values) **(Figure 17)**.

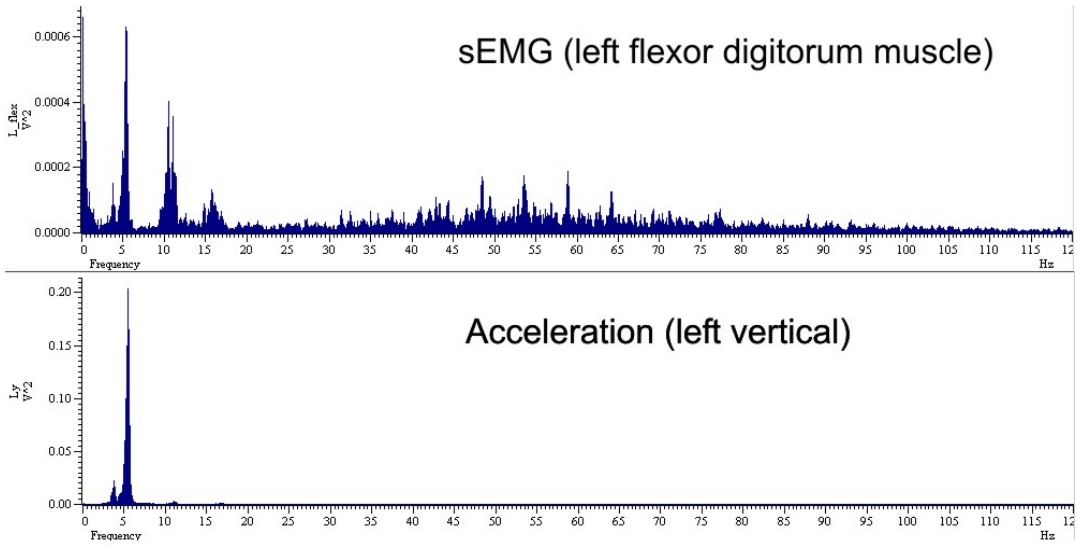

Figure 17. Power-spectrum of the accelerometry and the sEMG activity over left flexor digitorum muscle when tremor is present clinically. *Note that the peak frequencies of muscle activity (upper row) and tremor (lower row) is almost the same, 5.48 Hz.*

4. Intensity

Root mean square (RMS), also known as the quadratic mean, is a statistical measure of the magnitude of a varying quantity. It is especially useful when the signal can be both positive and negative. As RMS value is a measure of the power of the signal, it has a clear physical meaning and can estimate the force produced by the muscle **(Figure 18)**.

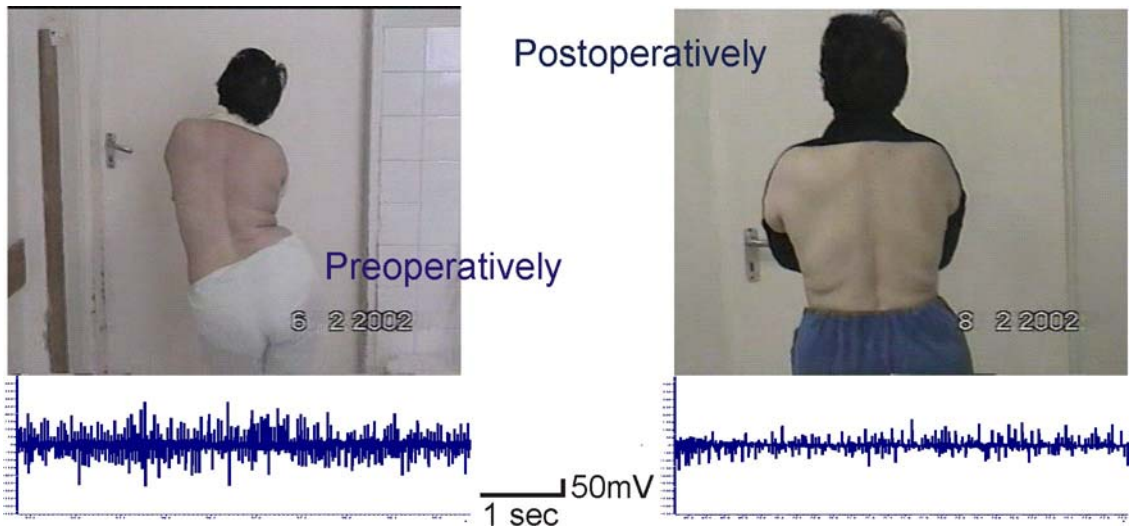

Figure 18. Quantification of the sEMG by the use of RMS. *In case of right axial hemidystonia, the pre- and postoperative RMS values of the sEMG signal recorded over the right paravertebral muscles were compared. In the particular case, the reduction of RMS by 67% demonstrated the efficacy of left pallidotomy in the elimination of dystonic muscle activity.*

5. Pattern of activation of antagonistic muscles

During tremor, the activation of antagonistic muscles can be synchronous or alternating. Alternating activation is typical for Parkinsonian rest tremor and the synchronous activation is often detectable in classical essential tremor. The activation of antagonist muscles can be objectively described by phase-delay. Values close to 0 radian suggest synchronous activation, while values around either +3.14 or -3.14 radians indicate antagonist activation.

Video-recording

As most international journals require video samples, if a tremor-related study is submitted for publication, I developed a software module, which is capable for recording video signals synchronously to the electrophysiological data. This approach is similar to the concept of video-EEG. During offline analysis, the examiner can compare the electrophysiological data to the video recording automatically.

The frame rate of digital video recording can be individually varied between 10-100 frames per second, which makes the program also suitable for eye-movement recordings. The only limiting factor in the video recording procedure is the upper sampling limit of the camcorder used.

Functional neurosurgical treatments for movement disorders

It took more than a century to get from the first surgical attempts to relief movement disorders (mainly Parkinson's disease) to the use of deep brain stimulation. Since James Parkinson described the nature of the "shaking palsy" in 1817, several neurosurgical attempts have been made. The main reason was that from the nineteenth century up until 1960s, surgery was the only therapeutic possibility because no effective pharmacological treatment existed.

Before the basal ganglia became recognized as the target for surgical treatment of movement disorders, various operations on the central and peripheral nervous system were developed based on insufficient knowledge and lacking appropriate surgical and imaging techniques[66]. Most procedures directly targeted the motor system, including the excision of the motor cortex[67], ablation or undercutting the premotor area[68] and the destruction of the pyramidal tract at various levels[69]. Therefore, the alleviation of movement disorders was usually achieved at the cost of hemiparesis[66].

Based on the work of Hassler[70] and Spatz[71], the importance of basal ganglia had been purposed for the development of PD. Meyers was the first to test this hypothesis and performed open surgical interventions on the caudate nucleus, the putamen, the pallidum and the ansa lenticularis[72, 73].

One of the most important revolutionary steps in the surgical treatments of movement disorders was the introduction of the stereotactic apparatus. Horsley and Clarke built the first stereotactic frame for animal experiments in 1906[74], which was adopted and improved for human neurosurgeries by Spiegel[75]. Spiegel and Wycis performed dorsomedial thalamotomies and pallidotomies with the aim to modify "afferent stimuli and emotional reactions"[76, 77]. Their method was soon adopted worldwide, and the first stereotactic ventrolateral thalamotomy was carried out by Mundinger to treat Parkinsonian tremor in Germany (1952)[78].

Most centers applied the technique of anteroventral pallidotomy in the fifties with disappointing long-term efficacy. The striking advance was made by a Swedish team led by Leksell, which moved the target into the posteroventral part of the pallidum, to the point where ansa lenticuralis arises. These operations gave dramatic long-lasting relief of tremor and rigidity[66, 79]. It was estimated that by 1965 more than 25,000 functional stereotactic procedures for Parkinsonism had been performed worldwide. However, the number of surgical operations rapidly dropped after introducing the levodopa and

consequently the discovery of posteroventral pallidotomy remained unnoticed until 1990s[66].

The interest in surgical treatments arose again when the limitations of long-term levodopa therapy became apparent, in particular with the late motor complications. The rediscovery of posteroventral pallidotomy by Laitinen had a major impact on the development of neurosurgical therapies (1992)[80, 81].

Meanwhile, the increased rate of morbidity after bilateral ablative interventions led to the introduction of chronic electrostimulation of deep brain structures. The technique of HFS was already used in the 1960s for more precise target detection before the permanent ablation was made[82]. A French group headed by Benabid applied the first chronic HFS as an adjuvant therapy to contralateral thalamotomy in 1987[83]. Deep brain stimulation soon replaced thalamotomy as a first choice surgical treatment for tremor[45].

The role of subthalamic nucleus (STN) in the pathogenesis of PD was first postulated in 1989[84], which led to the first electrode implantation to a human patient in 1993 by Pollak[85]. This was the first procedure, which could alleviate not only tremor, rigidity and drug-induced dyskinesia, but also bradykinesia. Since the mid-nineties, the implantation of deep brain stimulator to STN spread in the industrial countries and revolutionized the treatment of various movement disorders.

Surgical targets

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

1. **Ventral intermediate nucleus of thalamus (Vim).** The ablation or the HFS 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 rather good target to treat essential tremor.
2. **Internal part of globus pallidus (GPi).** The ventroposterior 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 antiparkinsonian medication, bilateral GPi stimulation is at disadvantage in treating PD. Currently, the stimulation of GPi plays a crucial role in the treatment of various primary and secondary dystonias.
3. **Subthalamic nucleus (STN).** The HFS and the ablation 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 unknown[86]. The stimulation of **pedunculopontine nucleus (PPN)** seems to be effective in Parkinsonian gait disturbances[87] and the **ventral oral anterior (Voa)** and **posterior (Vop)** nuclei might improve the Holmes' tremor[88] and certain dystonic disorders[89-91].

Ablative procedures

With the modern advances in neurosurgery, the lesioning approach seems to be a vestige of the past. However, in some developing countries, the deep brain stimulation is still unaffordable; therefore, the ablative procedures flourish because of its technical simplicity and inexpensiveness. Good example is the concept of subthalamotomy. The success of bilateral STN DBS encouraged certain centers to perform uni- or bilateral subthalamotomies: the short-term results of the procedure are similar with that of the stimulation[92].

Except for the final step, the procedure of ablation and deep brain stimulation is almost identical. With a stereotactic frame fixed to the skull, the patient undergoes a special MRI examination. The application of special 3D MRI sequences (e.g. magnetization prepared–rapid gradient echo MRI sequence, MP-RAGE) enables not only precise target localization, but also the visualization of the planned track of stimulating electrode. The latter is very important, because by avoiding the hit of sulci and ventricles, the chance of perioperative intracranial hemorrhage can be minimized. In case of ablation, an electrode capable for thermocoagulation at different temperatures is introduced. First, a trial, temporary coagulation is performed at 40 Celsius to test the efficacy and the development of side-effects in the awake patients. In case of good clinical efficacy and in the absence of side-effects, the permanent coagulation is finally made at 65 Celsius[31].

Deep brain stimulation

Deep brain stimulation has now become a widely used technique for the management of various drug-refractory movement disorders, including Parkinson's disease[93], dystonia[94] and various forms of tremor[95].

The deep stimulation consists of three different components:

1. implantable pulse generator (IPG),
2. connection cables, and
3. electrodes.

The IPG holds the battery for the stimulation and has the electrical circuits responsible for programmable current generation. Generally Soletra and Kinetra IPGs are available for uni- and bilateral stimulation, respectively **(Figure 19)**.

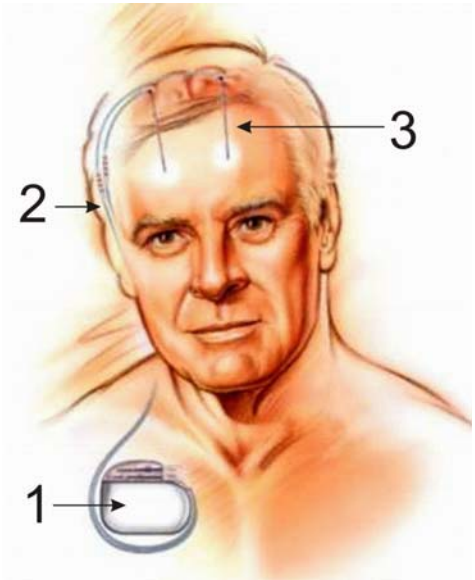

Figure 19. Newer types of impulse generators (e.g. Kinetra) are capable for the stimulation of both sides via two separate electrodes. *1= implantable pulse generator of Kinetra type; 2= connection cables; 3= quadripolar stimulating electrodes (Modified from: Medtronic Inc.)*

The stimulating electrodes for DBS have four contacts **(Figure 20)**. Based on the clinical efficacy we usually stimulate only one contact, which has the widest therapeutic range, the highest symptomatic efficacy, and does not produce any adverse reactions.

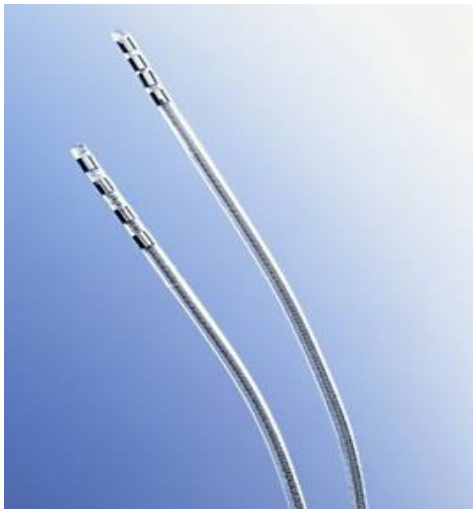

Figure 20. At present two different types of quadripolar electrodes are available for DBS. *Both of them have 4 pieces of 1.5 mm long contacts, but the intercontact distance is 0.5 mm for subthalamic nucleus stimulation and 1.0 mm for thalamic or pallidal stimulation. (Source: Medtronic Inc.)*

Among others, the most important advantage of deep brain stimulation is the adjustable stimulation parameters. During stimulation, high-frequency (usually 130 Hz) electricity is discharged at the electrode either in monopolar or bipolar mode. A typical setting for Parkinson's disease is the following: monopolar stimulation, 2.5-3.5 Volt amplitude, 130 Hz frequency and 60 μs pulse-width **(Figure 21)**.

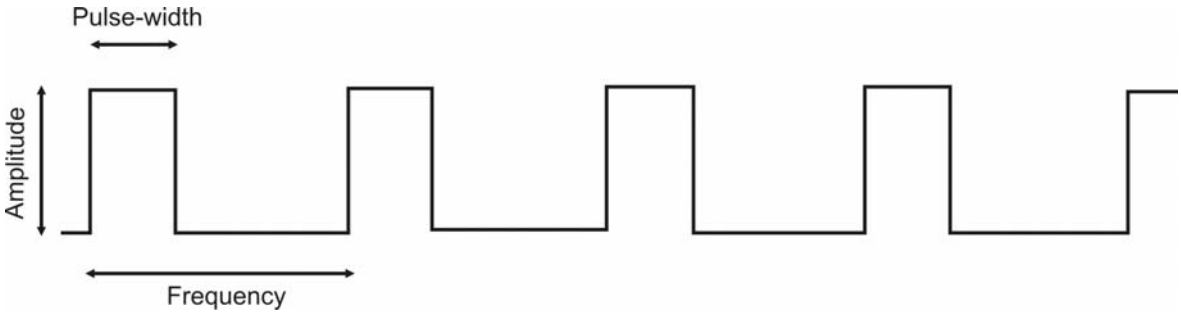

Figure 21. A schematic diagram illustrating the flow of current and the basic stimulation parameters. *Amplitude (voltage) is the most important parameter, which can be adjusted by either the physician or the patient. Conversely, the pulse-width and frequency of stimulation is usually adjusted solely by the physician.*

A unique feature of the deep brain stimulation is that the patient can also adjust the amplitude of stimulation depending on the clinical features. In case of bradykinesia or tremor; increasing the amplitude can resolve the problem; conversely in the case of dyskinesia amplitude reduction is necessary. After a proper training, the patient can learn how to manage on-off fluctuations, freezing and early morning dystonia.

The surgical planning of DBS implantation is basically the same to that of ablations. Unfortunately, the MRI imaging may have a small distorsion in the space, resulting in inaccuracy up to 1-2 mm. In case of subthalamic nucleus, the target is approximately 4x8 mm in length, therefore, we have to try to localize more precisely the target in vivo than the sole neuroimaging can do. Since 2005 in the Neurosurgical and Neurological Departments of University of Pécs, the microelectrode recording (MER) has been available. By analyzing the electrophysiological activity of the target area in 5 different tracks separated by 2 mm distance, we are able to select the best electrode position **(Figure 22 and Figure 23)**.

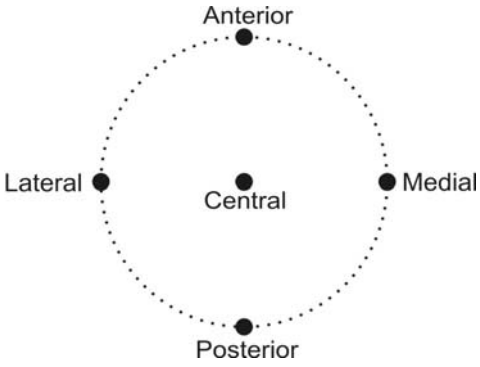

Figure 22. Five microelectrodes are introduced simultaneously by a stereotactic driver at each quadrant and the center of a 2 mm diameter circle. *The microelectrode recording of each electrode is evaluated during the operation and subsequently the best electrode position is selected.*

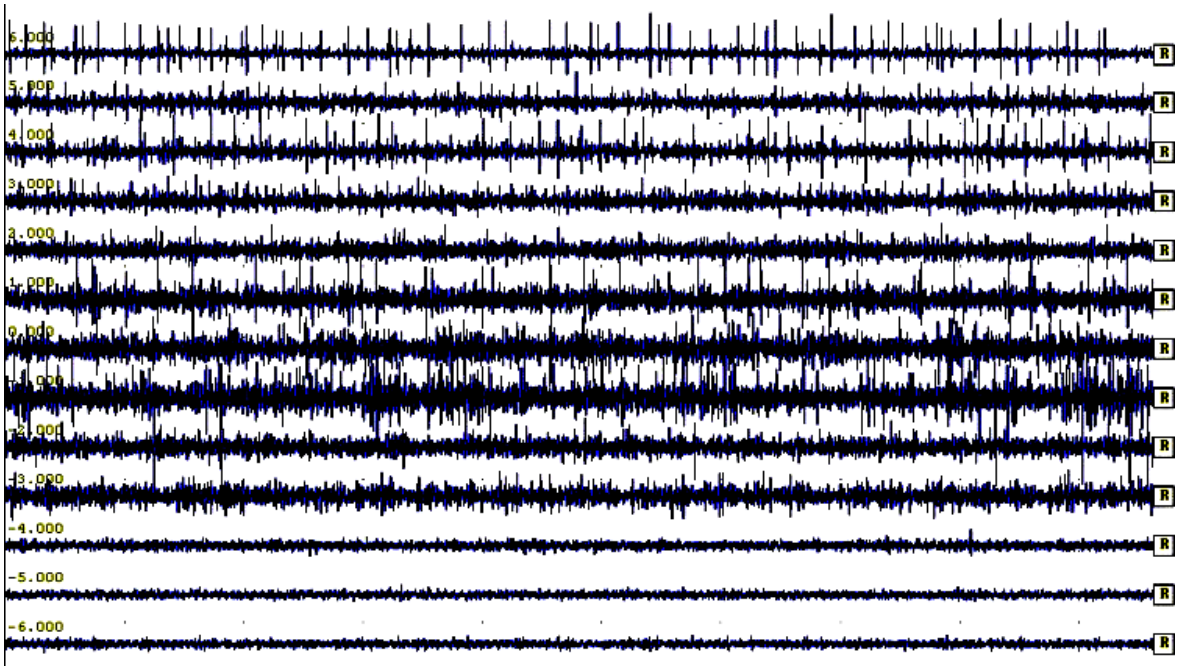

Figure 23. A sample from a microelectrode recording during subthalamic (STN) electrode implantation. *On the left side, the numbers present the distance from the planned target. Negative values represent proximal (closer to the surface of the brain) and the positive numbers indicate distal locations from the planned target. Between -6 and -4 mm typical white matter signal and zona incerta activity are presented. In the location between -2 and -3 STN border area was detected, whilst the activity presented in the range of -1 and +1 is typical for an overactive STN. In the range of +4 and +6, the activity of substantia nigra was recorded.*

After choosing the best electrode, we always perform functional testing, as well. The aim of trial-stimulation is to verify the clinical efficacy and determine possible side-effects in the awake patients. If the trial stimulation verifies good symptomatic relief without serious side-effects, the quadripolar stimulating electrode is placed instead of the microelectrode and subsequently the IPG is implanted in the subclavicular area[96].

Impact of neurosurgical treatments on tremor characteristics

Physiological tremor is a normal phenomenon derived from oscillators of the central nervous system, peripheral loop mechanisms, cardioballistic movements and modified by mechanical properties of limbs[97]. Using Fourier transform, physiological tremor reveals as an irregular, 5-12 Hz tremor with several, but often without any remarkably dominant peaks. In contrast, pathological tremor of PD and ET are characterized by regularity, presence of one dominant peak on the PS, and usually lower tremor frequency[98, 99].

Several studies have demonstrated that deep brain stimulator (DBS) implantation not only normalizes the intensity and regularity of pathological tremors, but postsurgical frequency increase in tremor EMG also occurs[52, 54]. Beside DBS, ablation of certain anatomical targets can also treat pathological tremors. Nevertheless, in 2-13% of the neurosurgical interventions the reduction of observed tremor is only transitory[100]. In the background of such long-term inefficacy, not surgical or methodological problems, but two pathophysiological phenomena can be suspected. Microelectrode recordings proved that the sole introduction of a microelectrode into most deep brain nuclei produces temporary suppression of symptoms, which is called the **microlesioning-effect**. Similarly, the **microedema** developing around the surgical trajectory can also induce temporary symptomatic relief. As the time goes by, the temporary result of microlesioning and microedema disappears, and consequently the clinical symptoms reappear. As the postoperative accelerometric changes of such effective and ineffective ablative treatments were not known in details, we performed an electrophysiological study focusing on these questions.

Materials and methods

Patients

The effect of 44 consecutive surgical procedures (32 ablations and 12 DBS implantations) of 33 patients (28 PD and 5 ET) was evaluated in prospective, long-term follow-up measurements. All patients underwent functional neurosurgical treatment (7 bilateral, 24 unilateral operations and 6 repeat operations because of unsuccessful intervention) to relieve tremor between December 2001 and December 2003. All PD patients had tremor dominant Parkinson's disease with Type I tremor. The diagnosis of ET and PD was in accordance with the current guidelines[2]. All examined patients had severe preoperative tremor. In addition, all ET patients had moderate, but visible resting tremor besides the serious postural-kinetic one. **(Table 2).**

Patient information				Operation information			Rest tremor frequency			Frequency shift	
Patient No	Age	Sex	Dis.	Operation type	Side	Success	Fr1	Fr2	Fr3	Shift1	Shift2
1	58	F	PD	Thalamotomy	R	+	5.42	8.75	8.43	3.33	3.01
2	62	F	PD	Thalamotomy	R	+	5.51	7.01	6.93	1.5	1.42
3	63	F	PD	Thalamotomy	L	+	4.88	5.81	5.94	0.93	1.06
4	70	M	PD	Thalamotomy	L	+	4.91	8.25	8.45	3.34	3.54
5	68	F	PD	Thalamotomy	R	+	5.19	7.52	7.61	2.33	2.42
6	67	F	PD	Thalamotomy	L	+	5.46	6.69	6.76	1.23	1.3
7	50	F	PD	Thalamotomy	L	+	5.77	6.94	7.01	1.17	1.24
8	71	F	PD	Thalamotomy	R	+	3.65	6.51	6.28	2.86	2.63
9	48	F	PD	Thalamotomy	R	+	4.93	6.63	6.76	1.7	1.83
10	68	M	PD	Thalamotomy	L	+	5.19	7.68	7.5	2.49	2.31
11	66	M	PD	Thalamotomy	R	+	4.5	7.76	7.77	3.26	3.27
12	71	M	PD	Pallidotomy	R	+	4.52	7.13	7.25	2.61	2.73
13	73	F	PD	Pallidotomy	R	+	5.58	6.82	6.79	1.24	1.21
14	54	F	PD	Pallidotomy	L	+	3.29	5.94	5.9	2.65	2.61
15	59	F	PD	Pallidotomy	R	+	4.48	5.49	5.39	1.01	0.91
16	74	M	PD	Pallidotomy	R	+	5.29	6.89	6.99	1.6	1.7
17	75	F	PD	Pallidotomy	R	+	6.01	7.01	7.12	1	1.11
18	63	M	PD	Pallidotomy	L	+	6.21	7.59	7.38	1.38	1.17
19	51	M	PD	DBS (STN)	R	+	4.32	7.05	7.12	2.73	2.8
20	66	F	PD	DBS (STN)	L	+	5.61	9.32	9.36	3.71	3.75
21	56	F	PD	Thalamotomy	R	+	5.82	6.72	6.71	0.9	0.89
				DBS (Vim)	L	+	5.4	6.81	6.76	1.41	1.36
22	58	M	PD	Thalamotomy	L	+	5.22	7.42	7.49	2.2	2.27
				DBS (Vim)	R	+	5.14	7.25	7.32	2.11	2.18
23	*49*	*F*	*PD*	*Thalamotomy*	*R*	-	*5.94*	*5.5*	*5.64*	*-0.44*	*-0.3*
				Pallidotomy	R	+ (reop)	5.64	7.25	7.76	1.61	2.12
				DBS (STN)	L	+	4.96	7.16	7.14	2.2	2.18
24	*60*	*M*	*PD*	*Thalamotomy*	*L*	-	*4.18*	*4.26*	*4.2*	*0.08*	*0.02*
				Thalamotomy	L	+ (reop)	4.22	7.25	7.38	3.03	3.16
				Thalamotomy	R	+	4.38	6.12	5.98	1.74	1.6
25	*40*	*M*	*PD*	*DBS (Vim)*	*L*	-	*4.87*	*4.99*	*5.03*	*0.12*	*0.16*
26	55	M	PD	Pallidotomy	R	+ (reop)	4.59	8.94	8.95	4.35	4.36
				DBS (STN)	L	+	4.56	8.63	8.65	4.07	4.09
27	41	M	PD	DBS (STN)	L	+ (reop)	5.11	8.31	8.29	3.2	3.18
28	51	F	PD	Pallidotomy	L	+ (reop)	3.94	7.25	7.45	3.31	3.51
29	67	F	ET	Thalamotomy	R	+	4.75	9.09	9.51	4.34	4.76
30	58	F	ET	Thalamotomy	R	+	6.01	9.12	9.25	3.11	3.24
31	51	F	ET	Thalamotomy	R	+	4.58	8.46	8.23	3.88	3.65
				DBS (Vim)	L	+	4.96	8.43	8.54	3.47	3.58
32	69	F	ET	Thalamotomy	R	+	3.68	6.59	6.69	2.91	3.01
				DBS (Vim)	L	+	3.74	6.71	6.72	2.97	2.98
33	*63*	*M*	*ET*	*Thalamotomy*	*L*	-	*5.15*	*4.88*	*5.1*	*-0.27*	*-0.05*
				DBS (Vim)	R	+	5.09	7.02	7.5	1.93	2.41
				DBS (Vim)	L	+ (reop)	4.98	6.98	6.86	2	1.88

Table 2. Detailed information of each patient, operation and observed frequency change. *Each subject has a unique ID. Fr1 is the frequency of rest tremor in Hz before surgery, Fr2 two days after surgery, Fr3 3 months after the intervention. Shift1 is the frequency-shift in rest tremor detected after operation (short-term change, difference of Fr2 and Fr1), Shift2 observed at control measurements (long-term change, difference of Fr3 and Fr1) compared to preoperatively recorded tremor. Efficacy of each surgical treatment was evaluated 6-12 months postoperatively by an independent investigator either as successful (+) or unsuccessful (-). Operations marked "+ reop"*

are successful repeat operations after an ineffective neurosurgical treatment. Three out of the re-operated subjects (Patient ID 26, 27, 28) had originally ineffective procedure before the start of this investigation.

Operative techniques

Unilateral ablation was performed on patients presenting symptoms mainly related to unilateral tremor unresponsive to medical therapy. In case of bilateral symptoms, unilateral ablation and contralateral DBS implantation were applied. A single ET patient received bilateral DBS implantation after an ineffective thalamotomy. Indication, anatomical localization, target selection, micro-recording and surgical procedure were carried out following current guidelines[81, 101].

Measurements

The ***baseline examination*** was performed 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 each occasion, 2 or 3 at least 7-15 minutes long measurements were recorded and FTMTRS[23] were applied at least 6 hours after drug withdrawal. Besides, all the patients were followed for at least 1 year by physical examination and applying FTMTRS, but in some cases without accelerometry.

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. The subjects were instructed to relax their forearms[102]. Calibrated accelerometers (ADXL-105, Analog Devices Inc., USA) were attached to the dorsal surface of both hands in the area of the third metacarpus.

Data analysis

Data processing and subsequent analyses were performed by using Spike2 script language (version 5.04, Cambridge Electronic Design Ltd., UK). After technical artifacts had been eliminated, the recordings were filtered by a low-pass filter with a cut-off frequency of 35 Hz. Although rest tremor in both hands was recorded, only the side contralateral to the intervention was analyzed. Six to twelve months after the surgery Interventions were evaluated by two independent investigators either as **'effective'** or **'ineffective'** based on the clinical symptoms and FTMTRS.

Characterization of tremors

1. Tremor reduction:

Fast Fourier Transform quantitatively describes the components of waveform data in the frequency domain and creates a plotting called power-spectrum, which can be converted to energy (i.e. intensity or power). Total power (TP) was calculated as the area

under the curve in the range of 3-15 Hz. Postsurgical improvement was quantified by a relative value:

Tremor reduction (TR) = (preoperative-TP) / (postoperative-TP).

Consequently, a larger value indicates more reduction in tremor.

2. Frequency of rest tremor (Fr)

Frequency of rest tremor was determined by comparing autocorrelation and power-spectrum with the original accelerometric waveform data to ensure accurate results. The interpeak intervals of autocorrelation curve and the length of a periodic tremor oscillation measured on the accelerometric recording were identical; their inverse value gave the dominant frequency of tremor.

3. Irregularity of tremor (approximate entropy, ApEn):

Irregularity was quantified by approximate entropy (ApEn), a method measuring the unpredictability of fluctuations[103]. Recording containing many recurring patterns has a relatively small ApEn, i.e. a more regular value, contrary to a less predictable process, which has a higher, i.e. a more irregular value[60]. During ApEn calculations, the suggested parameters were used ($m = 2$, $r = 0.2 \times SD$)[54].

4. Morphology of power-spectra:

Morphology of PS was qualified by the number of peaks in the range of 3-15 Hz. A peak in PS was defined as an increase of at least 3 frequency bins from the surrounding bins on either side.

Statistical analysis

All statistical analyses were carried out using SPSS software package (version 11, SPSS Inc, Chicago, USA). Statistical significance level was set to 5%. Since none of the critical variables were normally distributed, non-parametric Wilcoxon signed ranks test and Mann-Whitney test were performed.

Results

Changes in Parkinsonian rest tremor after effective neurosurgical treatments

Thirty-two operations to control Parkinsonian tremor in 28 patients were considered to be effective and analyzed. First, we examined whether the type of intervention (ablation vs. DBS implantation) and the target of ablation (thalamotomy vs. pallidotomy) may influence various characteristics of resting tremor.

1. The *intensity of tremor* (total power) decreased significantly on the second postoperative day ($p<0.001$). Both clinical and electrophysiological improvements (tremor reduction, TR) were maintained and detectable 3 months after surgery in all patients.

However, a small but significant increase in intensity of rest tremor compared to the short-term values was observed in all cases 3 months after surgery, indicating that part of the postoperative effect was transitory (short-term TR: 46.7 vs. long-term TR: 28.9). In addition, the long-term effect of DBS implantation was significantly better compared to ablative treatments in PD patients (TR: 48.5 vs. 23.9), although short-term data were similar **(Figure 24)**. When thalamotomy and pallidotomy were compared, neither short- nor long-term tremor reduction was different (p>0.05).

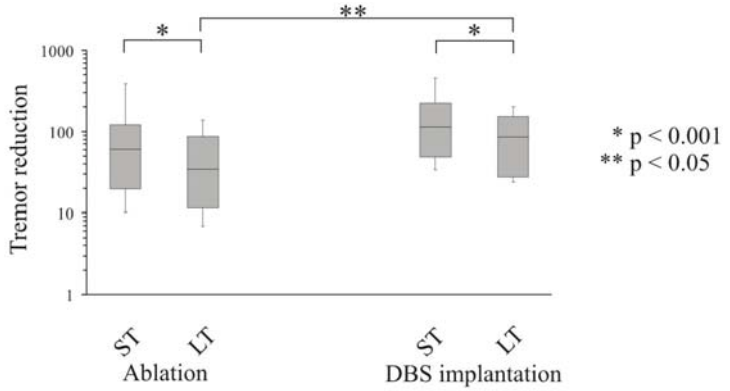

Figure 24. Short-term (ST) and long-term (LT) tremor reduction after effective interventions in PD patients were compared. *Since tremor reduction values did not follow the normal distribution, the lower and upper borders of boxplot represent the 25th and 75th percentiles, while the middle line indicates the median. Error-bars show the minimum and maximal values.*

2. An *increase in frequency* (range: 0.90-4.35 Hz) of rest tremor was detected on the second day and three months later in all cases **(Table 2)**. In contrast to intensity of tremor, the value of short- and long-term frequency increase did not differ significantly (2.20 vs. 2.22 Hz). The type of surgical procedure **(Figure 25)** and the target of intervention also did not significantly influence the size of the frequency changes. This uniform increase in frequency was confirmed by 4 individual cases, where the effect of unilateral DBS implantation combined with contralateral ablation was similar **(Figure 26)**.

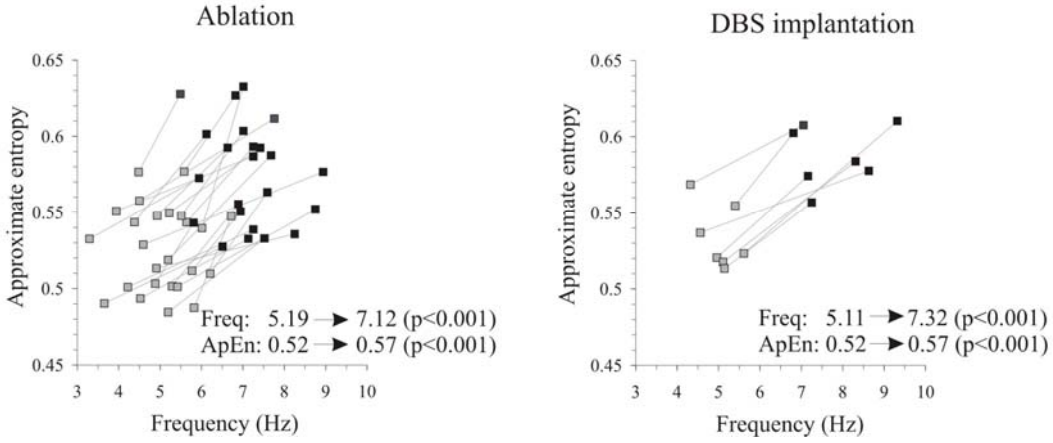

Figure 25. Pre- and postoperative rest tremor ApEn is plotted against tremor frequency in cases of ablations and DBS implantations. *Preoperative values are marked by gray squares, while the 2nd day postoperative values are indicated by black squares.*

3. Both short- and long-term *irregularity of tremor* (ApEn) were significantly increased after effective operations (from 0.52 to 0.58, $p<0.001$), suggesting that the tremor became more irregular similar to physiological tremor. Neither the type nor target of intervention influenced the size of ApEn increase **(Figure 25)**.

4. While *power-spectrum* of the original pathological tremor consisted of a single peak with its harmonics, 3-9 peaks appeared after effective treatments suggesting attenuation of the pathological oscillators **(Figure 26, Table 3)**.

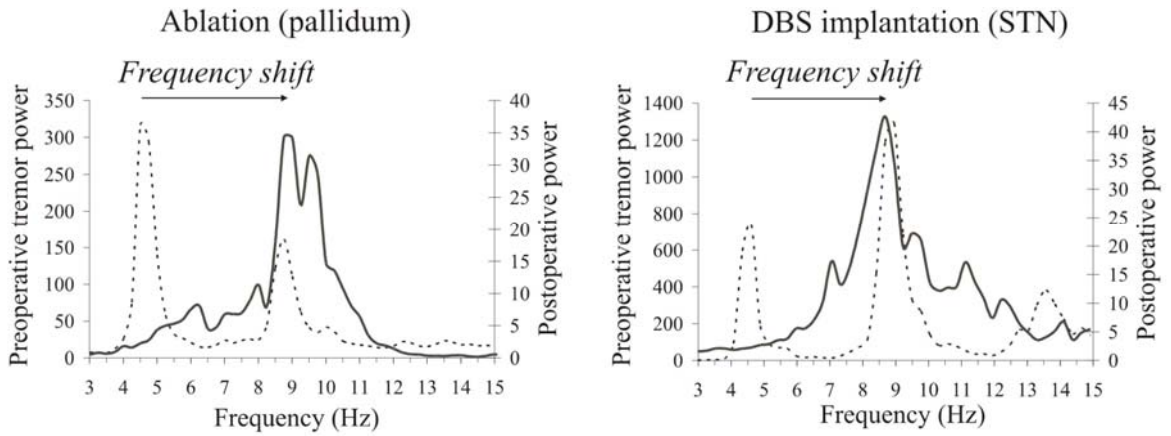

Figure 26. Pre- and postsurgical power-spectrum of a PD patient after effective pallidotomy (left panel) and contralateral DBS implantation to STN (right panel) is presented. *Presurgical tremor measurements are indicated by dotted lines, while tremor examinations on the 2nd postoperative day are represented by solid lines. The increase in frequency after surgery is indicated by horizontal arrows. Pre- and postoperative tremor powers have different scales.*

	Total power[a]		Frequency		Number of peaks on PS	
Surgery	Effective	Ineffective	Effective	Ineffective	Effective	Ineffective
Preoperative	N/A	N/A	5.12 (40/40)	5.01 (4/4)	2.1 (40/40)	2.2 (4/4)
Postoperative 2 days	2.12%[b] (40/40)	1.41%[b] (4/4)	7.14[b] (40/40)	4.93[c] (4/4)	5.4[b] (40/40)	2.2[c] (4/4)
Postoperative 3 months	3.34%[b] (40/40)	47.62%[b,c] (4/4)	7.19[b] (40/40)	5.06[c] (4/4)	5.8[b] (40/40)	2.0[c] (4/4)
Postoperative 6-12 months	3.93%[b] (21/21)	89.76%[c] (4/4)	7.21[b] (21/21)	4.87[c] (7/7)	4.9[b] (21/21)	2.1[c] (7/7)

Table 3. Characteristics of postsurgical rest tremor after ineffective operations compared to effective interventions. *The intensity of tremor, the tremor frequency and the number of peaks on power-spectrum are compared between effective and ineffective neurosurgical interventions. For definitions of tremor characteristics and the efficiency of surgery refer to text.*
[a]Postoperative total power is given in relative value as the percentage of preoperative-TP
[b]Statistically significant change compared to presurgical value ($p<0.01$)
[c]Statistically significant difference compared to effective group ($p<0.01$)
N/A = not applicable

Taking together, increase in frequency, irregularity and change in the morphology of PS were observed after effective surgery irrespective of the type and target of interventions, while quantitatively the long-term tremor reductive effect of DBS implantation was significantly better **(Figure 24)**.

Postoperative changes in resting essential tremor

In PD patients, neurosurgical treatments had a qualitatively similar, significant impact on electrophysiological properties of rest tremor. To determine, whether the described findings were disease specific, we analyzed the effects of 8 interventions on resting essential tremor**.** Although ET is regarded as postural-kinetic tremor, moderate resting essential tremor were both visually and accelerometrically detectable at rest in all cases. The presence of this symptom allowed the comparison of the effects on rest tremor in both ET and PD after thalamotomies.

Remarkably, short- and long-term tremor reductions after thalamotomy were not statistically different between PD and ET. However, the size of frequency shift was significantly larger in ET than in PD (3.12 Hz vs. 2.22 Hz, median), indicating that the etiology of pathological tremor may influence the magnitude of frequency-shift **(Figure 27)**.

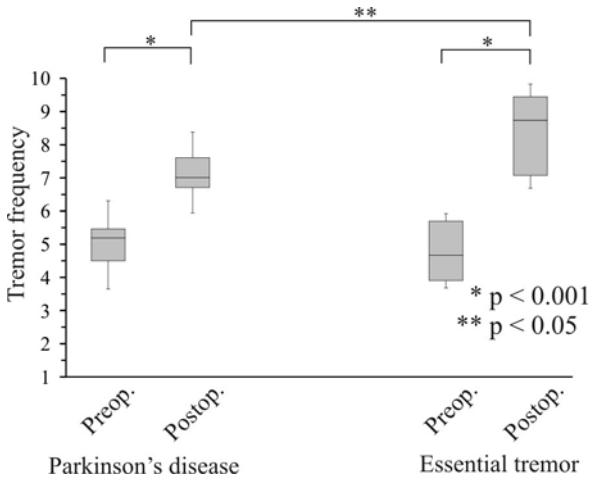

Figure 27. Rest tremor frequency before and after successful thalamotomies in PD and ET. *The postoperative frequency values are significantly increased in all individual cases (p<0.001); however, the size of increase were significantly larger in the ET group (p<0.05).*

Although an increase in postoperative ApEn was detected similarly to PD, this increase was significantly higher in ET as well. The preoperative PS of rest tremor in ET was very similar to that observed in PD, characterized by a single dominant peak with its harmonics **(Figure 28)**. The pattern of power-spectra was characterized by appearance of several peaks after thalamotomy indicating a similar attenuation of pathological oscillators as observed in PD.

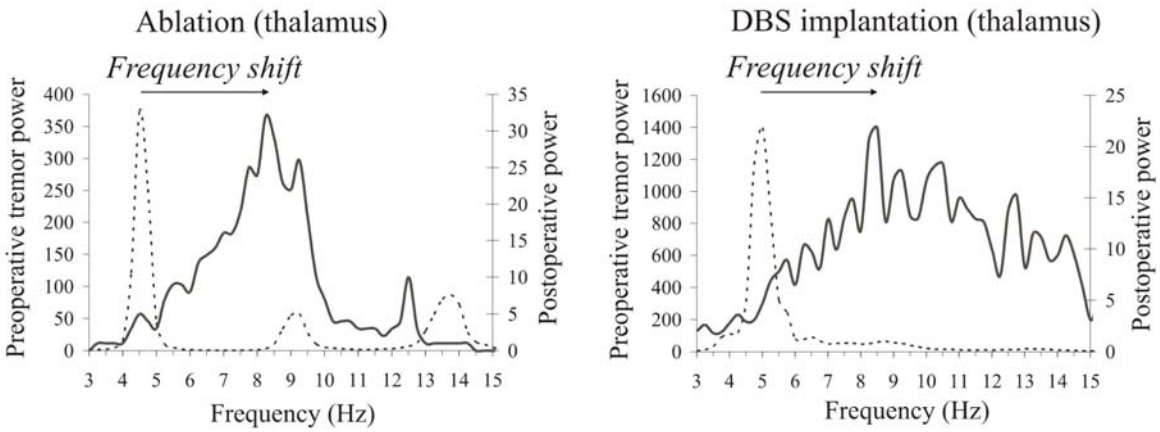

Figure 28. Pre- and postsurgical power-spectrum of an ET patient after thalamotomy and contralateral DBS implantation is presented. *Presurgical tremor is indicated by dotted line, while tremor on the 2nd postoperative day is represented by solid line. Increase in frequency after surgery is indicated by horizontal arrows. Pre- and postoperative tremor powers have different scales.*

Since these data altogether indicated qualitatively similar, but quantitatively different postoperative changes in different rest tremors, next we examined tremor after unsuccessful operations.

Differences between 'effective' and 'ineffective' neurosurgical interventions

First, the power-spectra were analyzed in 7 cases (6 PD and 1 ET), where clinical tremor re-appeared 6-12 months after surgery indicating ineffectiveness of the applied intervention. A single dominant peak, similar to untreated tremors, characterized the postoperative PS morphology in all 7 cases **(Figure 29, Table 2, Table 3)**.

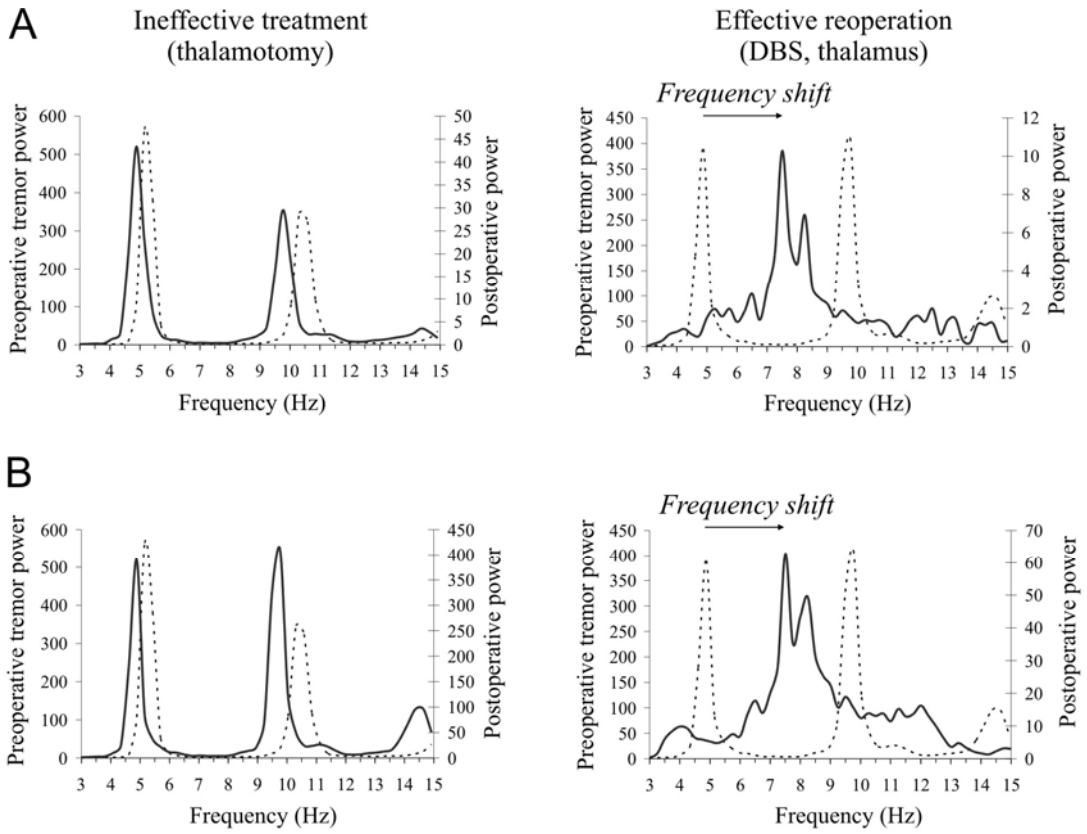

Figure 29. The figure illustrates both the short (A) and long-term (B) postoperative power-spectra compared to the preoperative ones in a single case after an ineffective thalamotomy and an effective re-operation. *The left panel indicates ineffective thalamotomy, while the right panel shows effective re-operation of the very same patient. Presurgical tremor is indicated by dotted lines, while the tremor observed on the second postoperative day (A) and the third postoperative month (B) is represented by solid lines. Of note, pre- and postoperative scales are different (preoperative: left axis, postoperative: right axis). Horizontal arrows indicate the postoperative frequency increase. Similar changes have been recorded in PD patients after effective re-operations.*

This unchanged PS morphology suggested that unsuccessful operations did not alter the rest tremor properties. To this end, we examined all the other characteristics of rest tremor in 4 patients after ineffective surgery (3 PD and 1 ET). Unexpectedly, two days after the surgical procedures tremor was significantly reduced similarly to effective operations. However, 3 months later, the postoperative rest tremor intensity increased to near the baseline. More importantly, a lack of increase in frequency was evident as early as on the second postoperative day, despite of clinical improvement (frequency-shift: -0.09 Hz, statistically not significant) **(Table 2, Figure 29)**. Similarly, ApEn and the morphology of PS also remained unchanged.

Altogether, these data indicated that these tremor characteristics remained unaffected after ineffective operations.

Discussion

In the present study, we compared the effects of different effective and ineffective neurosurgical treatments on resting Parkinsonian and essential tremor. Both DBS implantations and obsolete ablative treatments were examined to get a more complex view of tremor genesis.

Postsurgical changes in PS morphology, frequency-shift and irregularity of rest tremor after ablative treatments have not been analyzed in details so far. By examining the effects of 25 effective ablative treatments on Parkinsonian rest tremor, an increase in frequency, ApEn and number of peaks on power-spectra was detected, indicating that postoperative tremor became more similar to physiological tremor. Although effective surgical treatments changed all examined characteristics in a similar way, a small, but statistically significant worsening in tremor intensity was detected electrophysiologically between the short- and long-term states. Meanwhile, neurological examination and FTMTRS did not show any worsening. This phenomenon may be due to the vanishing of the microlesioning effect. By the comparison of thalamotomy and pallidotomy, no significant difference could be observed in any of the analyzed parameters.

When effects of DBS implantations were examined, we noticed an increase in number of peaks on the power-spectra similar to ablations. In addition, an increase in frequency and ApEn of rest tremor was found confirming previous data and indicating higher irregularity in tremor genesis[52, 54].

Beside better long-term tremor reductive effect of DBS implantations against ablations, no qualitative or quantitative difference could be observed in any other examined tremor characteristics. This was also confirmed in individual cases of PD and ET patients, where unilateral ablation combined with contralateral DBS implantation resulted in analogous changes. Consequently, ablation and DBS implantation may similarly influence the pathological oscillators responsible for tremor.

In order to determine, whether the described postoperative changes are disease-specific or general, resting essential and Parkinsonian tremors were also compared after thalamotomy. In the observed ET cases pathological rest tremor could be detected even visually beside the dominant postural-kinetic one, which allowed us to compare rest tremor properties of different etiologies. Remarkably, the etiology of tremor determined the size of frequency-shift and ApEn change indicated by a significantly larger increase in ET. Presumably thalamotomy might have similar impact on the pathological oscillators and synchronization in both diseases.

To fully analyze postoperative changes, characteristics of rest tremor after ineffective interventions and their repeat operations were also examined. Interestingly, the postoperative short-term tremor reduction did not differ significantly between effective and

ineffective treatments. However, an increase about 20 times larger was observed three months later in unsuccessfully compared to the successfully treated cases, which became more prominent in the 12 months control measurement **(Table 3)**. Remarkably, in contrast to successful operations, frequency of rest tremor, PS morphology and ApEn remained unchanged even on the second postoperative day, while clinical tremor was equally reduced in both cases. Thus, whichever factor is responsible for considerable tremor reduction; it suppresses solely the intensity of rest tremor, but has no effect on other tremor characteristics. This differential effect on morphology of tremor may predict the outcome of surgery very early, even when short-term tremor reduction still does not indicate ineffectiveness. In other words, not the reduction of tremor intensity, but the change of tremor frequency, irregularity and power-spectrum morphology may indicate the further effectiveness of surgery.

Two theories have been suggested to explain the phenomenon of tremor frequency and ApEn increase observed after DBS implantation in PD and ET patients[52, 54]. 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 ablation and DBS, suppression rather than resetting oscillators seems more probable.

Several theories suggest that the highly synchronized pathological tremor generators are superimposed on the physiological oscillators[98, 99]. 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, irregularity (ApEn) and multi-peaked power-spectrum.

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 frequency, the low ApEn value and a single dominant peak on power-spectrum indicate that post-surgical 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 not sufficient to alter other accelerometric properties (e.g. frequency, entropy and number of peaks on the power-spectrum).

Summing up, our results suggest that effective neurosurgical treatments result in a qualitatively uniform pattern in tremor characteristics. The multi-peaked rest tremor power-spectrum, the increase in irregularity and frequency could be due to attenuation of pathological oscillators and the release of previously suppressed physiological tremor generators. Moreover, the presence of these changes might be an immediate indicator of the effectiveness of neurosurgical treatments relieving tremor.

Bilateral effects of unilateral deep brain stimulation

Unilateral deep brain stimulation (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. Using the Fahn-Tolosa-Marin Tremor Rating Scale (FTMTRS)[23], Ondo, et al.[104] demonstrated a clinically slight, but statistically significant tremor reduction on the ipsilateral (nontarget) side. Nevertheless, they suspected exclusively mechanical causes rather than a direct CNS effect of the DBS.

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 (5 Parkinsonian tremor, 8 essential tremor, 2 multiple sclerosis, and 1 tremor associated with mitochondrial encephalomyopathy), we found only a single case where the unilateral thalamic DBS had clinically improved both the bilateral limb and head tremor. As the FTMTRS itself might be insufficient for a distinction between active and passive tremor reductions, 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. Her case was published previously with regard to patient history, tremor characteristics and surgical treatments[26].

Briefly, at the age of 48, she experienced pharmacoresistant bilateral, predominantly postural-kinetic limb and head tremor after several stroke-like episodes. The tremor affected the right side more seriously. The amplitude of the tremor was moderate at rest, higher in a postural situation and very serious under kinetic conditions. After a 1-year progression, the tremor had increased to such a level that she was no longer able to walk and take care of herself. 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, surgical treatment was offered. A left thalamotomy performed at the age of 50 resulted in a marked tremor

reduction and 1 year later a DBS electrode was implanted into the right Vim[26]. With the stimulating parameters 0-C+, 130 Hz, 60 µs, 1.4 V, permanent and pronounced tremor reduction was achieved[26].

Tremor recording

This investigation was performed in 2007, 4 years after the DBS implantation. Written informed consent was obtained from the patient for all the examinations described below and for the presentation of video recordings at scientific congresses or in scientific journals. Beside physical examination and the assessment of FTMTRS, we also applied simultaneous sEMG and accelerometry. Tremor was investigated in various positions: Rest tremor was examined while the patient was sitting in a chair with her forearms supported by the arms of the chair. The hands were able to dangle freely, and the patient was asked to relax her musculature.

To record postural tremor, one of the upper limbs was maintained against gravity, while the other was in a resting position. For kinetic tremor, both goal-directed (finger-to-nose) and non-goal-directed (e.g. elbow extension and flexion) maneuvers were also performed, while the other hand was in resting position.

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. Signals were digitalized at a sampling rate of 1000 Hz (Power1401, Cambridge Electronic Design Ltd., UK). The system was also capable of capturing a video signal synchronized with the electrophysiological recordings.

Data analysis

The exact method of data processing and subsequent analyses were described previously. Technical artifacts were eliminated using Spike2 (version 6.03, Cambridge Electronic Design Ltd., UK). Subsequently, the data were filtered by applying a band-pass Butterworth digital filter (4^{th} order; the passband was 0.7-35 Hz for the accelerometric recordings and 50-350 Hz for the sEMG). Finally, sEMG signal was rectified[34]. Three parameters were determined:

(1) The **frequency** of tremor was determined by analyzing autocorrelation curve[54].

(2) The **intensity of tremor** was considered as the area under the power-spectrum in the range of 3-15 Hz[105, 106].

(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.

For qualitative analysis, the electrophysiological data and the video recording were investigated simultaneously, such as a video-EEG technique used in epilepsy monitoring.

Results

If the **DBS was on**, no tremor could be detected visually in any of the examined positions, while the frequency of rest and postural tremors was relatively high (right: 8.12 Hz, left: 7.96 Hz). Tremor-related burst activity did not appear in the sEMG recordings.

After the **stimulator was turned off**, however, bilateral limb tremor and head tremor appeared on both sides **(Figure 30)**. In the resting condition, the frequencies on the two sides were slightly different (right: 5.41 Hz vs. left: 5.22 Hz) and this difference increased when the right kinetic condition was considered (right: 6.29 Hz vs. left: 5.28 Hz). Furthermore, the intensity of right kinetic tremor was also much higher than that of left (1268 and 889 milli-g^2, respectively). Switching on DBS abolished the tremor bilaterally.

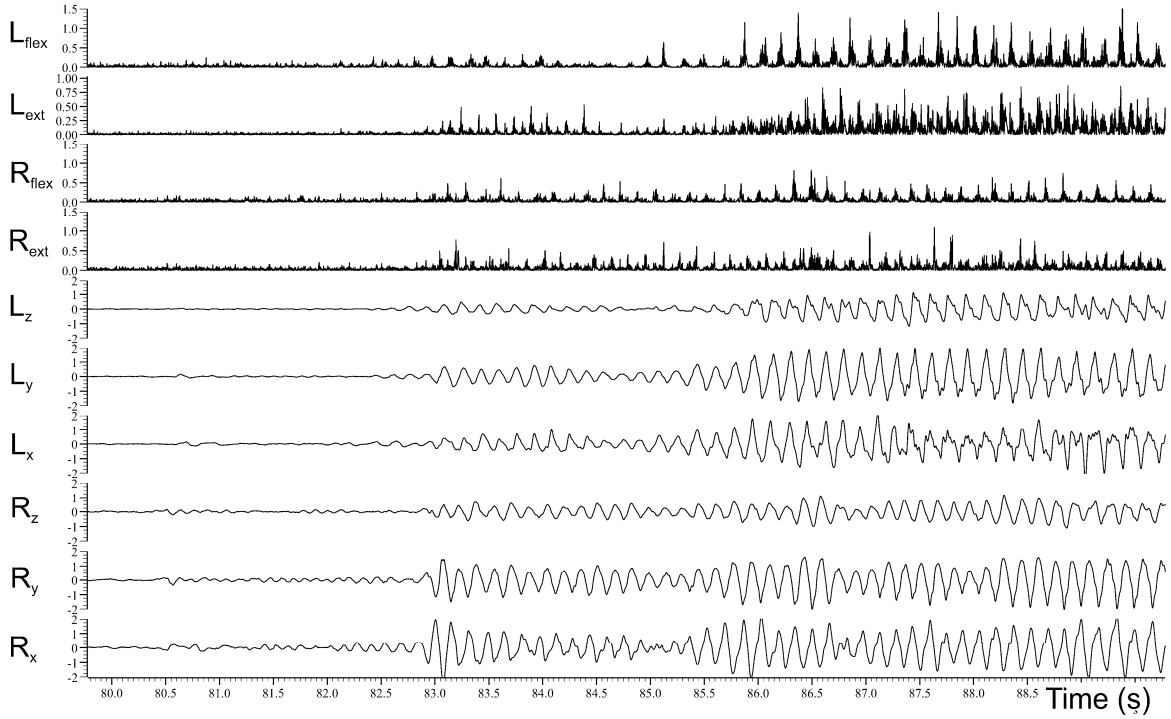

Figure 30. A simultaneous accelerometric and rectified surface EMG recording (sEMG) is presented. *The right Vim DBS was turned off at 80.5 seconds. L=left, and R=right side. In the accelerometric recordings, the indices x, y, z indicates the 3 different planes. Flex and ext denote sEMG of flexor and extensor forearm muscles. One y-axis unit equals with 1 gravity (9.807 m/s^2).*

Discussion

A recent paper by Chung, et al. on the bilateral effects of unilateral subthalamic DBS described an approximately 20% reduction in the UPDRS part III ipsilateral subscores[107]. 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. The frequency of the right hand tremor was almost 1 Hz higher in kinetic condition.
3. 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 tremor was more pronounced than the left rest tremor. Consequently, these right kinetic tremors cannot simply reflect the mechanical overflow of the left side.
4. When the stimulator was turned off, head tremor also developed. Previous studies have clearly demonstrated that bilateral thalamic stimulation is usually required to achieve the most consistent improvement in this symptom[108, 109].
5. Other previous studies have revealed that Vim DBS increases the tremor frequency[54, 105]. In our case, when the right Vim DBS was switched on, the tremor frequency of both hands increased.

The physical examination and the electrophysiological data suggest active CNS 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 affected by the previous thalamotomy, 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. For a better understanding of the bilateral effect of unilateral DBS, further investigations (e.g. functional neuroimaging) may have been required. Functional MRI, however, cannot be performed for technical reasons[110] and the patient refused other neuroimaging methods involving the use of radiotracers. Learning the pathophysiology of the deep brain stimulation could yield in better therapeutic options.

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 severely affected Parkinson's disease (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

The patients

Twenty-three right-handed patients with idiopathic PD[11] participated in the study (age: 61.3 ± 5.7 years, 13 males, disease duration 8.9 ± 2.1 years). In all cases, subthalamic electrodes were implanted bilaterally with similar optimal stimulation settings (unipolar, 3.10 ± 0.42 V, 60 μs, 130-135 Hz). 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 ± 4.8 years, 8 males) who did not have any kind of neurological disorder or dementia either. In accordance with the Regional Ethical Committee, all the participants gave their written informed consent to participate in the study; they all received scores of >27/30 points in the Hungarian version of the Mini-Mental State Examination[111] to exclude dementia.

Cognitive ERP recording

Cognitive ERP measurements were carried out at least 6 months (on average 11.1 ± 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[112] and the technical review by Polich[113]. Briefly, the subjects were seated in a comfortable chair in a quiet room with their eyes open. In accordance with the international 10/20 system, silver/silver-chloride electrodes were

applied (Fz, Cz, Pz, Oz; F3, C3, P3, F7, T3, T5, F4, C4, P4, F8, T4 and T6) and their resistance was kept below 5 kOhm. Each of the electrodes was referenced to the common A1/A2, and the ground electrode was placed over the forehead. Additionally, electrooculographic activity was recorded to identify eye movement artifacts during the offline analysis[114]. 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). The time constant was 1 s, while the gain was set individually to capture the optimal EEG signals. Apart from an anti-alias (500 Hz low-pass) analog filter, no other hardware filtering was performed during the recording.

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 to achieve a comfortable stimulus presentation rate. 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.

All measurements were carried out after at least 12 hours (usually overnight) drug withdrawal in order to eliminate the aliasing-effect of dopaminergic therapy on the P300 characteristics[115, 116]. The DBS turned off **(DBS-OFF)** and DBS turned on **(DBS-ON)** states were evaluated in a random sequence. Following a short learning period in each state, two recordings were made, each containing at least 50-60 valid relevant triggers (signals that were followed by button pressing). Recordings were accepted for further analysis only if the online ERP curves of both recordings were well-configured and reproducible[112]. Between the DBS-ON and DBS-OFF recordings, there was a 5-10 minutes long break for refreshing, but the electrode positions remained unchanged and their resistance was re-checked.

Data analysis

All offline measurements and data modifications were carried out with Spike2 (version 6.03, Cambridge Electronic Devices Ltd, Cambridge, UK). Since all recordings were identified by a randomly generated alphanumerical ID, neither the identity of the subjects nor the nature of the measurements (DBS ON vs. OFF) was known to the investigator (NK).

Technical and eye-movement artifacts were first removed by using a semi-automated method under visual guidance. On the basis of current guidelines[112, 113], a bandpass

infinite impulse response digital filter[46] was constructed and applied with the bandpass of 0.3-30 Hz (Butterworth type, 4th order).

During ERP calculations (offset: 200 ms, epoch length: 1000 ms), 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[112]. 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.

Statistical analysis

All statistical analyses were carried out with an SPSS software package (version 15, SPSS Inc, Chicago, Illinois). The statistical significance level was set at 5%. Since none of the critical variables were distributed normally, nonparametric Wilcoxon signed ranks and Mann-Whitney U-tests were performed. For correlations, Kendall's tau was calculated.

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 ($p<0.05$). Further, neither the amplitudes nor the latencies differed significantly over any other electrodes. Detailed information on the P300 latencies can be found in **Table 4** and a sample analysis is illustrated on **Figure 31**.

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 stimulator 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.

	DBS-OFF			DBS-ON			Control group		
Elect-rode	Median	25th percentile	75th percentile	Median	25th percentile	75th percentile	Median	25th percentile	75th percentile
Fz	355.61	342.519	404.576	364.429	324.589	401.638	315.634	309.864	379.857
F8	375.2	348.762	420.243	398.869	346.314	429.301	367.545	324.325	412.353
T4	371.283	341.907	402.618	366.387	328.198	405.272	339.864	301.244	378.973
T6	379.117	341.907	407.514	370.304	327.219	397.722	352.348	298.654	378.96
Cz	380.096	341.907	406.534	355.616	325.87	386.95	329.874	297.684	368.965
F4	378.138	341.907	411.43	379.794	327.22	420.033	350.134	312.342	399.863
C4	369.369	343.621	405.066	361.002	343.11	399.19	340.632	323.146	375.678
P4	367.366	341.418	402.618	372.752	344.845	404.576	345.674	323.464	380.463
Pz	374.906	348.517	403.842	369.325	344.845	400.659	334.975	306.785	371.864
F7	403.597	335.053	431.994	413.597	349.731	434.599	382.14	315.863	413.453
T3	369.52	332.795	409.227	371.773	342.152	406.304	346.231	316.435	379.865
T5	375.2	342.397	398.946	377.158	331.136	401.638	350.134	303.846	379.783
Oz	385.482	353.168	429.301	368.346	354.357	397.722	342.357	325.675	386.532
F3	361.491	339.085	404.086	384.963	341.908	406.779	353.562	315.749	382.462
C3	369.325	342.513	401.149	358.554	338.236	398.864	332.134	309.853	375.443
P3	368.239	338.48	400.17	360.512	318.896	404.087	339.874	302.453	379.563

Table 4. Detailed information of P300 latencies in the Parkinsonian group (both DBS turned on and off modes) and the control group. *All values are given in milliseconds.*

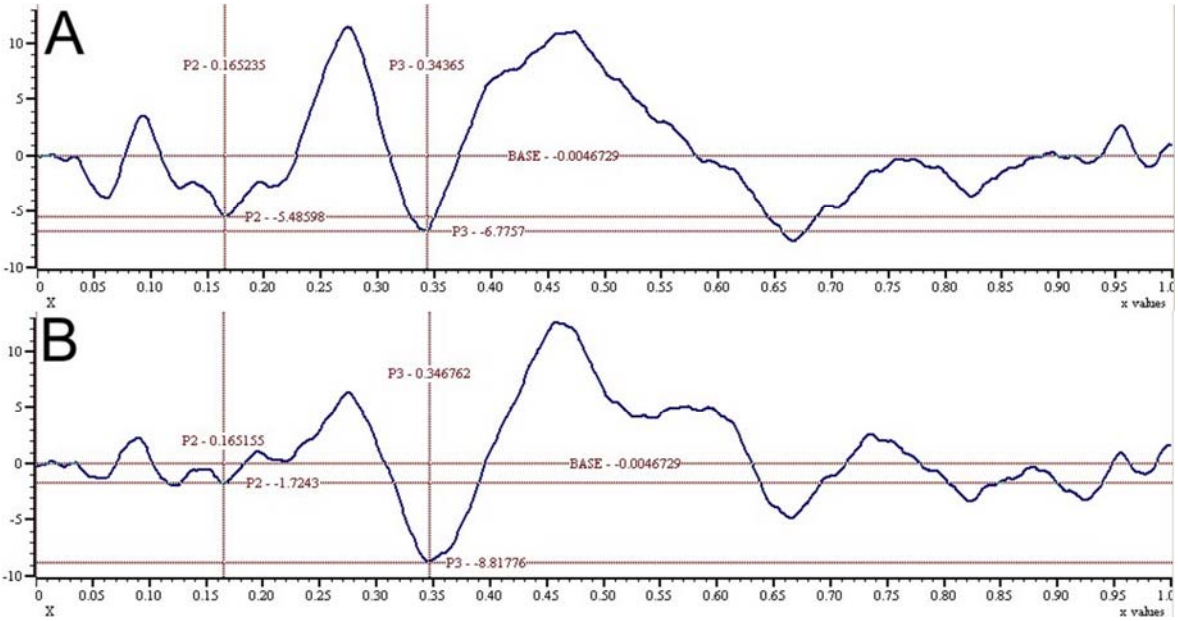

Figure 31. Event-related potential over the Cz electrode of a PD patient with bilateral subthalamic deep brain stimulation turned on (A) and turned off (B). *Time is presented in s, the voltage in μV. The latency and the amplitude of the P300 and P200 components are marked with cursors showing the exact values.*

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 5**).

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

Table 5. Comparison of reaction time, duration of button pressing, percentage of valid signals and the occurrence of mistakenly pressed buttons in both the Parkinsonian and the control group.

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 5**).

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 5**) 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 5**), than they did in the DBS-ON state.

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 process[117-119].

By making use of long-latency ERPs, we set out to test various cognitive factors, including attention, memory and speed of stimulus evaluation time[113]. 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 channels. The difference in P300 latencies between non-demented, advanced Parkinsonian patients and age-matched control subjects is a well-established phenomenon[120, 121], that is unrelated to the DBS itself.

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. As previous studies have demonstrated a relation between the P300 amplitudes and performance intelligence quotients and the motor items of the Functional Independence Measure[122], it may be assumed that the higher stimulation voltage affects not only the motor performance, but also the P300 amplitudes.

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.[123] 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 ± 93 ms; DBS-OFF: 671 ± 98 ms). Similar 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 ± 36 ms; DBS-OFF 440 ± 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±0.42 Volt, 60±0μs vs. 2.4±0.76 V, 84.4±12.1 μs) 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 conditions by applying a sampling frequency rate of 250 Hz with a 100 Hz digital low-pass filter, and a constant interstimulus interval (2 seconds), which may also have had an impact on the ERP configuration[112, 124].

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[124-129] 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 by comparing the latencies and amplitudes. However, the topographic distribution of the P300 components and the attentional and motor performance aspects seem to be changed in response to DBS. Likewise 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 of 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. I 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 also developed a 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 tremor, 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. Ablation is still a widely applied technique in the developing countries to treat certain movement disorders. However, in approximately 10-20% of the cases the long-term outcome is not satisfactory due to the microlesioning effect. The introduction of an electrode into the target (e.g. Vim or GPi) even in the absence of ablation, still can have an immediate, but temporary relief of symptoms called microlesioning-effect. Because intraoperatively, the neurosurgeon cannot distinguish the effect of ablation from the microlesioning-effect based on purely clinical examination, in some cases inadequately small ablations are performed resulting in unsuccessful outcome. Based on the presence or absence of the frequency-increase, I could identify successful and unsuccessful cases as early as on the second postoperative day. These results may help in identifying the inefficiency during the operation, thus can dramatically improve surgical effectiveness.
4. Beside ablative treatments, the consecutive tremor analysis of deep brain stimulation also yielded in important results. I was the first to prove the possibility of the bilateral effect of unilateral thalamic (Vim) stimulation.
5. I made the first attempt to evaluate 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 mental functions.

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