Surgical treatment of epilepsy and effects of ANT-DBS on interictal heart rate variability

Doctoral PhD thesis

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I. Introduction

Epilepsy is the second most common, potentially severe neurological disease after stroke, affecting approximately 50-60 million people worldwide. According to epidemiological data, 0.5-1% of the population in Hungary have epilepsy (60-80 thousand people). The lifetime probability of an epileptic seizure is even more common (5%), but only 10-20% of these seizures are caused by epilepsy. About 60% of epilepsy patients suffer from focal epilepsy syndrome. In nearly 1/3 of these patients, antiepileptic therapy for epileptic seizures does not lead to seizure freedom or a significant reduction in the number of seizures. In these pharmacoresistant cases, epilepsy surgery should be considered.

4.5% of all epilepsy patients (0.003% of the population) can potentially benefit from surgical intervention. 30-85% of patients who undergo surgery will be seizure-free, depending on the epilepsy syndrome and the exact location of the epileptogenic zone. Surgical treatment of epilepsy can be a very successful therapeutic modality in selected patients.

The indication for surgical intervention is established by a multimodal epilepsy surgical team, whose members are: neurologists with expertise in epilepsy and electrophysiology, neuroradiologists, neurosurgeons, neuropsychologists and psychiatrists. For patients suitable for surgical intervention, the most favorable postoperative results can be achieved if the operation is performed as early as possible.

The aim of epilepsy surgery is to completely remove or disconnect the epileptogenic zone while preserving the eloquent cortex.

The goals of the presurgical evaluation are to identify the epileptogenic zone fully and avoid operative morbidity associated with a focal cortical resection. Standard components of the surgical evaluation include detailed neurologic history and examination, neuropsychologic testing, routine electroencephalography (EEG) recordings with standard activating procedures, inpatient long-term video-EEG monitoring in an epilepsy monitoring unit, high-resolution brain MRI, and functional and metabolic imaging using positron emission tomography (PET) and/or single-photon emission computed tomography (SPECT). Preoperative formal speech and language testing, visual field examinations and invasive diagnostic modalities are also performed in selected patients.

Thus multimodal presurgical evaluation is only feasable in interdisciplinary epilepsy centers. Figure 1. shows the steps of the preoperative evaluation.

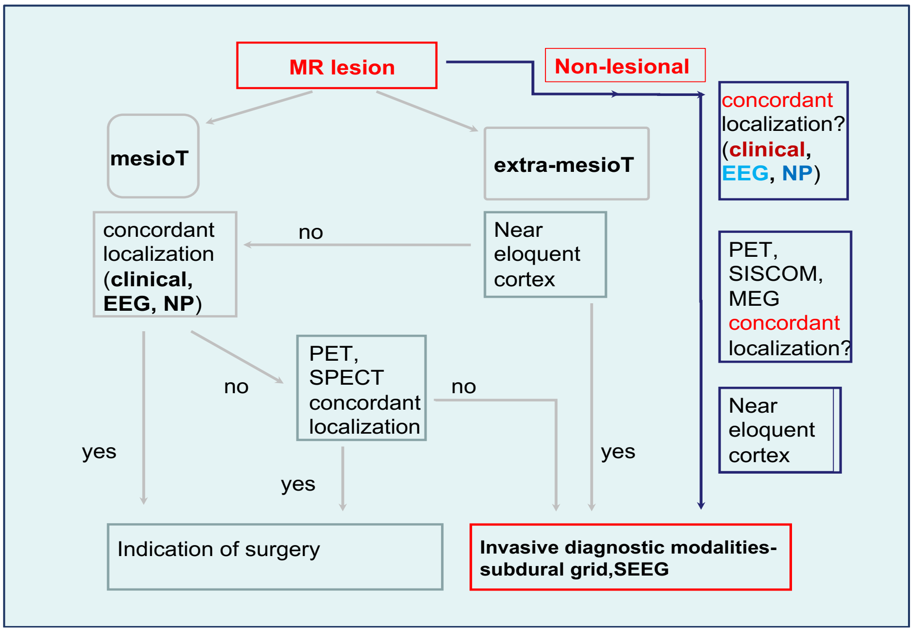


Figure 1. Strategy of preoperative evaluation

(S.Naochtar, I. Borggraefe/Epilepsy and Behavior 15 (2009)66-72))

II. Aim

1.,

We aimed to study postoperative outcome, quality of life, change of social role and employement status of patients with drug resistant epilepsy who underwent multimodal preoperative evaluation and resective epilepsy surgery between 05/2005 and 05/2016 in the Epilepsy Center of Pecs.

We also evaluated postoperativ outcome of patients who underwent neuromodulation (DBS, VNS) therapy in the Epilepsy Center at Pecs between 2005 and 2014.

2.,

In our second study, we investigated interictal HRV changes both while awake and during N1- or N2-stage sleep in patients with drug-resistant epilepsy who underwent ANT-DBS implantation at two Hungarian epilepsy centers (Budapest and Pecs), between 2011 and 2019.

III. Postoperative outcome of surgical interventions for epilepsy between 2005 and 2016 at the Epilepsy Center of Pécs

1. History of epilepsy surgery in Hungary

Epilepsy surgery operations in Hungary are currently performed in 3 main centers: Budapest, Pecs and Debrecen.

The current work was founded by internationally known predecessors. From the 1950s to the 1970s, the publications of Hullay [1-2] at the Neurosurgery and Neurology Clinic in Debrecen, and Fenyes [3] at the National Institute of Neurosurgery (OKITI) report on the results of early epilepsy surgery.

Peter Halasz is associated with the organization of the modern presurgical evaluation in Hungary, which relies on the rapidly renewed imaging modalities in the 1980s.
Based on the summary of Rásonyi and colleagues [4], the more than 100 epilepsy surgeries performed at the OPNI-HIETE Epilepsy Center until 1999 resulted in postoperative seizure freedom in 67–79%.

Kelemen and colleagues reported on long term seizure outcome and influencing factors of patients who underwent anterior temporal lobe resection in between 1985 and 2001 in the National Institute of Psychiatry and Neurology Budapest (OPNI) and National Institute of Neurosurgery Budapest (OKITI) [5], while the results of the Epilepsy Center of Budapest (cooperation of OKITI, OPNI, Bethesda Children's Hospital, Szent Janos Hospital and Szent Istvan Hospital) was published by Balogh and colleagues [6].

Epilepsy surgery was introduced by István Környei at the Neurological Clinic at Pecs. The Epilepsy Center at Pecs – providing presurgical evaluation and epilepsy surgery as daily routine – was established in 2005 with the cooperation of the PTE Neurological Clinic and Neurosurgery Clinic, as well as the Institute of Behavioral Sciences and Biology and the Diagnostic Center at Pecs.

2. Aim

We aimed to study postoperative outcome, quality of life, change of social role and employement status of patients with refractory epilepsy who underwent multimodal surgical evaluation and resective epilepsy surgery between 05/2005 and 05/2016 in the Epilepsy Center of Pecs.

3. Methods

We retrospectively analyzed patient records of pre- and postoperative regular check-up examinations. We also collected data prospectively via phone calls and questionnaires.

The multimodal preoperative evaluation in drug resistant patients consisted of recording a thorough patient history, performing scalp -EEG, in-patient video-EEG-EKG monitoring (duration of 2-10 days), MRI examination with epilepsy protocol (1.5–3 Tesla) [7], neuropsychological testing and selected patients also underwent positron emission tomography.

Multidisciplinary team of neurologists with expertise in epileptology and electrophysiology, neurosurgeons, neuroradiologists, a neurophyschologist and psychiatrist indicated the resective surgical operation after evaluating the results of the preoperative examinations, considering the risks and benefits of the surgery, estimating the probable epileptological, kognitive, psychiatric and social outcome and possible complications. Patients were informed about the recommendation of the team and decided to undergo or reject the surgery.

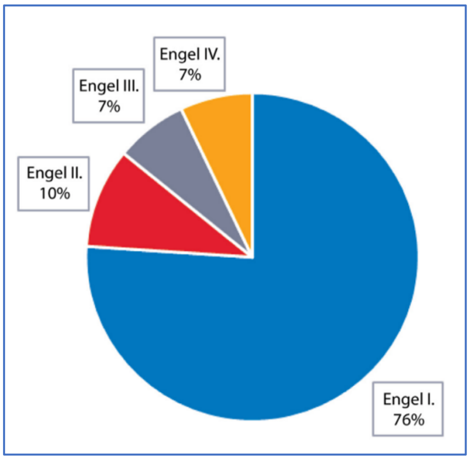
The postoperative seizure outcome was evaluated using the Engel classification [8]. Follow-up MRI and neurophsychological examinations were carried out 6 months and 2 years postsurgically. Seizure outcome of patients reported in the study were evaluated in regular check-ups, additional data were collected via phone calls and questionnaries. We evaluated not only postoperative seizure outcome, but also social well-beeing, quality of life and employement status.

Drug discontinuation was considered after a minimum of 2 years seizure freedom.

4. Results

Between 05/2005 and 05/2016, overall 72 patients underwent resective epielpsy surgery in the Epilepsy Center of Pecs. There were no significant gender-difference- (54% female, 46% male). The mean age at time of surgery was 37 years (SD: 11,39), the youngest patient was 9 and the oldest 63 years old. Mean disease duration before resective surgery was 21 years (SD: 14,00), in 52 patients mean disease duration was > 10 years.

We evaluated postoperativ outcome in 71 patients. The mean follow-up to report postoperativ outcome was 5,2 years (1-2 years was the shortest period of follow up, in this group we had 19 patients, further we had 3-5 years follow-up in 18 patients and 6-10 years follow up in 33 patients).



76% of our patients were completely free from disabling seizures – (Engel Class I). 10% achieved almost seizure freedom, (rare disabling seizures, Engel Class II). 10% had worthwhile improvement (Engel Class III). 7% experienced some- but not worthwile improvement of seizures, while 7% had no worthwile improvement (Engel IV/a, b). See summary of results in Figure 2.

Figure 2. Postoperative outcome after resective epilepsy surgery

In patients with Engel Class I 37 % was able to discontinue antiepileptic medication completely. Before operation this group was tretaed with 1-4 different antiepileptic drugs. With the exception of 3 patients the dosis of the antiepileptic medication and polytherapy could succesfully be reduced postsurgically in all other patients as well in this cohort.

The histological examination confirmed in 37% of patients hippocampal sclerosis (HS), in 28% tumors (cavernoma, glioma, cholesteatoma, disembrioplastic neuroepithelial tumor [DNT], teratoma), in 14% focal cortical dysplasia (FCD), in 8% dual pathology of hippocampal sclerosis and focal cortical dysplasia, in 6% multiple pathologies (for example HS and occipital cavernoma), in 4% comlex developmental anomaly, and in 3% of patients the histology confirmed no epileptogenic lesion [9].

Examining complications of resective epilepsy surgery we found, that only 3 out of 71 patients were suffering from permanent complications of surgery, 2 had partail loss of visual field and one were complainaing of headaches and dizziness.

Furthermore we examined how employement status of patients with epilepsy included in our study changes after resective epilepsy surgery. Employement status not only influences quality of life after epilepsy surgery, but also important to consider when organising rehabilitation for patients after epilepsy surgery. 61 of our 71 patients disclosed employement status. 33 patients were employed (54%) and 28 were not (46%).

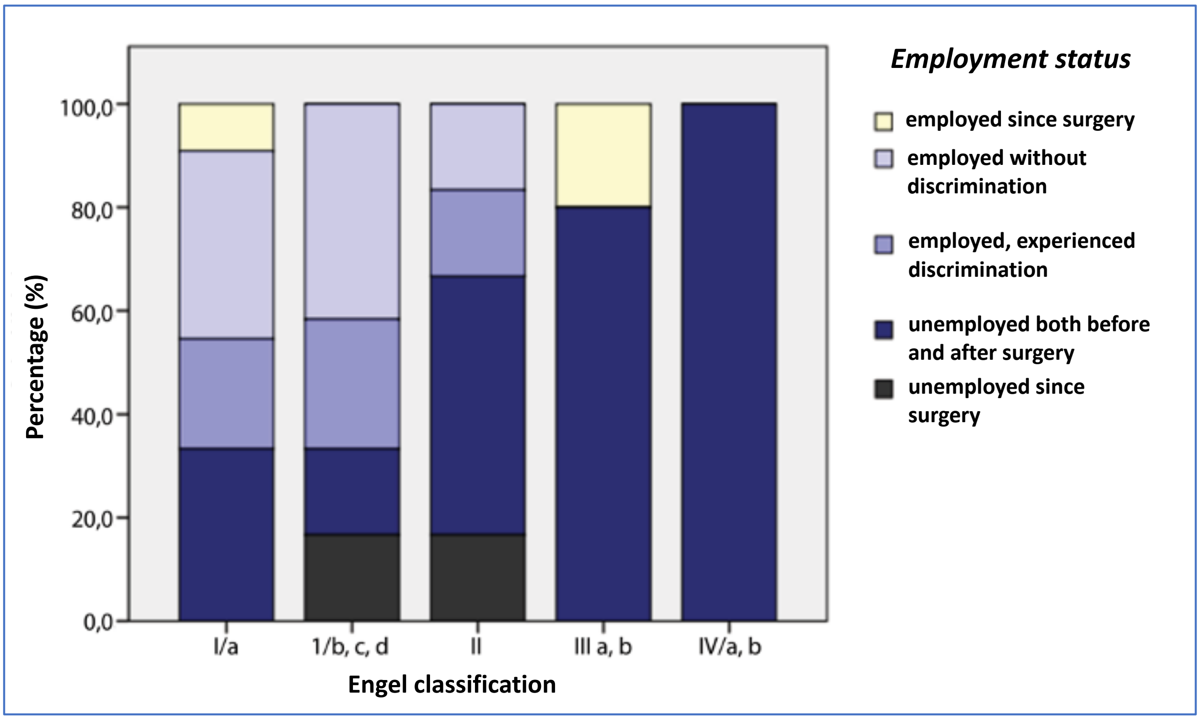


Figure 3. Employment outcomes after resective epilepsy surgery

Quality of life can be significantly influenced by occupational status after epilepsy surgery. 67% of patients in group Engel Class I/a were employed. 9% of them got employed after resective epilepsy surgery resulting in seizure freedom, 37% were before and after surgery also employed without experiencing discrimination, while 21% of them reoperted, that they suffer under discrimination at work. 33% of patients in Engel Class I/a group were unemployed before and after epilepsy surgery, even though they achieved seizure freedom.

In the group of patients with Engel Class I/b, c, d outcome also 67% were employed. 41% of these patients reported to work without discrimination, while 25% experienced discrimination at work. 33% of patients in this group were unemployed.

34% of patients in group Engel Class II were employed, half of them experiencing discrimination, half of them reportedly not, and 66% of this group were unemployed.

In the group of Engel Class III 20% of patients became employed after resective surgery while 80% stayed unemployed in spite of worthwile improvement in their siezure status. None of the patient in group Engel Class IV was employed. Figure 3. shows the employement outcome.

There was no gender gap in employment in our cohort. We report the results of 61 patients - 31 female and 30 male. 52% of our female cohort and 56% of our male cohort were employed. There was also no geneder difference shown when examining postoperative seizure outcome in gender subgroups.

Comparing patient groups Engel Class I (free from disabling seizures) and Engel Class II-IV (not free from disabling seizures) we found, that seizure freedom significantly influences employment outcome ($p<0,01$, Fisher's exact test). 67% of patients free from disabling seizures (Engel Class I) were employed while only 19% of patients not free from disabling seizures (Engel Class II–IV).

5. Discussion

The management of patients with epilepsy is focused on controlling seizures, avoiding treatment side effects, and maintaining or restoring quality of life. Clinicians should assist in empowering patients with epilepsy to lead lifestyles consistent with their capabilities [10-12].

Depending on location of the epileptogenic zone and etiology of epilepsy patients achieve postoperative seizure freedom in 50-90% after resective epilepsy surgery, which immensely impacts quality of life [13].

Postoperative outcome of patients who underwent resective surgery in our epilepsy center show a tenedeny similar to international results- 76% of all patients after resective epilepsy surgery and 78% of patients with temporal lobe epilepsy became seizure-free [14-18], proving that effectiveness of epilepsy surgery does not depend on the country or region.

After resective epilepsy surgery, 54% of the patients in our cohort were employed, one third of them reported to suffer under discirmination at workplace inidacting that epilepsy continues to be associated with stigmatization and social isolation. The unawareness of the society of psychosicial and medical aspects of epilepsy manifested in rejecting or discriminating patients with epilepsy increases patient's disease burden, social and financial burden of epilepsy. Postoperative seizure outcome is one of the main factors influencing quality of life and employement status. 67% of the patients in group Engel Class I were employed, while only 34% in Engel Class II, even less- 20%- in Engel Class III and none of the patients in Engel Class IV.

While seizure freedom after resective epielpsy surgery is an important factor in influencing quality of life of patients [19], similarly important factors are howener social support or social rejection, stigmatization [20]. Results of postoperative seizure outcome reflect international seizure freedom rates in Hunargy -testifying the effectiveness of epilepsy surgery-, shortcomings in social education and psychosocial rehablitation of patients with epilepsy increases social and financial burdens of epilepsy. Also disease burden of patients who already achieved seizure freedom, but due to years of social isolation and stigmatisation, the complexity of their psychosocial background prevents from a responsible and successful self-management of reintegration [21].

Individualised rehabilitation for patients with epilepsy is well organised in several specialised centers in Europe. These centers offer individualised in-or outpatient rehabilitation programs based on interdisciplinary approach (involving neurologist, neuropsychologist, psychiatrist, social worker, speech therapist, physiotherapist, career coach, educational counselor [22]. These programs include the work-up of cognitive status, memory disorders, neuropsychiatric examination, psychological counselling, psychiatric care in the case of psychiatric comorbidity, patient and family education, work-up and optimalisation of environmental conditions, the individual assessment of the epilepsy disease [23-26]. This special complex rehabilitation includes social rehabilitation, career counselling, coaching for a job interview, personalized exercise rehabilitation, counseling on sports opportunities, diagnosis and treatment of cognitive and speech disorders, increasing the workload at work, increasing mental endurance, and stamina training [23-26].

Epilepsy centers are to provide state of the art interdisciplinary presurgical evaluation, surgical intervention and psychosocial rehabilitation. Management of patients with epilepsy must include consideration of the psychosocial dimensions of the disorder. Patients with epilepsy additionally to medical and psychiatric comorbidities suffer from loss of independence, underemployment, poorer social status, decreased physical activity compared to unaffected population. Epilepsy affects each patient in a unique way, also patients differ in their capacity to understand various aspects of the disorder. Clinicians should tailor discussions to clarify the impact of the condition on the patient's quality of life, social and employment status and expectations of the treatment plan.

Besides routine neurological follow-ups specialised centers should consider psychosocial aspects of epilepsy. Psychosocial treatments should be targeted for development in Hungary and needs to be integrated into the treatment flow of epilepsy centers to provide rehabilitation aiming at reintegration of epilepsy patients in the society [27].

IV. Effects of anterior thalamic nucleus DBS on interictal heart rate variability in patients with refractory epilepsy

1. Introduction

Heart rate variability (HRV) time- and frequency-domain parameters have been researched extensively under various physiological and pathological conditions. HRV parameters, which reflect the state of the autonomic nervous system, are used to evaluate the balance of the sympathetic–parasympathetic nervous system, assess general well-being, mental and physical stamina, and the life expectancy of a person [28]. Furthermore, HRV is a potential biomarker of sudden unexpected death in epilepsy (SUDEP) [29]. Reduced HRV is associated with maladaptive responses to mental and physical stress, shortened life expectancy, and an increased risk of SUDEP, arrhythmia, sudden cardiac death, acute myocardial infarction, and diabetic neuropathy [28].

Studies that have investigated ictal [30] and interictal HRV have suggested that sympathetic overactivity occurs in most forms of epilepsy [31], while autonomic dysregulation appears to be most severe in patients with temporal lobe epilepsy and drug-resistant epilepsy [32]. With longer disease duration, pathologic epileptogenic networks become established, so that HRV does not change significantly even after successful resective surgery [33-35]. Neuromodulation therapies with constant stimulation may alter such pathological networks. Positive effects of vagal nerve stimulation (VNS) on HRV [36] have been observed. An increased reduction in seizure number has been reported as a long-term effect of deep-brain stimulation (DBS) [33]. Anterior thalamic nucleus-DBS (ANT-DBS) therapy may also modulate HRV in the long run.

Epileptogenic network, HRV, and autonomic nervous system changes in patients with epilepsy who had undergone resective epilepsy surgery/VNS have been investigated by numerous studies [32-36], however, only a few have investigated the effects of ANT-DBS. ANT-DBS was described by the SANTE study as an evidence-based alternative to further drug therapy in patients who were not candidates for resective surgery [37]. Reportedly, 54% of the patient population investigated in the SANTE study had seizure reductions of at least 50% by 2-years post-operatively, with DBS therapy response defined as a seizure reduction rate of 50% post-operatively. Although the therapeutic potential of ANT-DBS is promising, its efficacy varies widely.

Although executive function [38] and default mode network [39] changes have been reported in patients who underwent ANT-DBS and have been proposed as possible predictors of DBS therapy outcomes, the underlying physiological mechanisms related to effective stimulation delivery are still not well understood. A previous study described autonomic nervous system changes that occurred after DBS in the periaqueductal grey (PAG) and subthalamic nuclei [40] however, to the best of our knowledge, no previous study has assessed interictal HRV in patients who underwent ANT-DBS implantation. A study investigating the effects of ANT-DBS on the autonomic nervous system may help unravel the underlying physiological mechanisms related to effective stimulation delivery and may facilitate optimized target engagement.

2. Aim

In this study, we aimed to investigate HRV changes in patients with drug-resistant epilepsy who underwent ANT-DBS implantation at two Hungarian epilepsy centers, between 2011 and 2019. We recorded HRV both while awake and during N1- or N2-stage sleep, as the diurnal variations in HRV may have considerable relevance for people with seizures [41-44], following the Task force of ILAE [32].

3. Methods

Thirty patients with therapy-resistant focal epilepsy who underwent presurgical evaluation between 2006 and 2019 and DBS implantation between 2011 and 2019 were included in our study. Based on presurgical examinations, including video-electroencephalography (EEG) and magnetic resonance imaging (MRI), all patients were excluded from resective surgery. The mean age of the patients at surgery was 35.3 ± 10.28 years (range: 17–64 years), and the mean disease duration was 22.2 ± 9.8 years (range: 5–43 years). Disease onset was on average 13.43 ± 8.18 years (range: 0.1–34 years). Of the 30 patients, 20 were female and 10 were male. All patients underwent standard clinical electrocardiographic (ECG) evaluations and had normal sinus rhythm. 19 of the 30 patients were treated at the Epilepsy Center of the National Institute of Clinical Neurosciences in Budapest, and 11 were treated in the Epilepsy Center at the University of Pecs, Hungary.

There were no significant differences between these two patient populations in terms of clinical, social, or demographic characteristics or treatment strategies; therefore, we evaluated them as one cohort in the statistical analysis. Patients were followed-up according to the clinical routine, completely independently from the present study. Therapy outcomes were collected during clinical visits based on seizure diaries. Responders were defined as a minimum of 50% seizure reduction at 1 year after implantation, as compared to the pre-operative seizure count.

The study was approved by the local ethics committees of the University of Pecs (Pecsi Tudomanyegyetem Klinikai Kozpont Regionalis Kutatasetikai Bizottsag) and the National Institute of Clinical Neurosciences at Budapest (OKITI Etikai Bizottsag, Intezmenyi Kutatas Etikai Bizottság OKITI) IKEB Iktatoszam:9/2020. Informed written consent was obtained from all participants, in accordance with the Declaration of Helsinki. (World Medical Association et al., 2013) [45].

Procedure and materials

DBS implantation

Surgical planning was performed using Medtronic Framelink 5 Stealth Station software or Medtronic S7 Planning Station and Cranial Software (Medtronic, Minneapolis, MN, USA) on high-resolution contrast T1, axial STIR, coronal STIR, and 3D-gradient echo sequences, with two inversion recovery times, by visualizing the mamillothalamic tract as an anatomical guide. Surgery was performed under general anesthesia using the CRW Precision™ Arc System (Integra Life, Princeton, NJ, USA) or the Leksell Stereotactic Frame (Electa Inc., Atlanta, GA, USA). DBS electrodes (Medtronic 3387 for transventricular and Medtronic 3389 for paraventricular or transventricular approaches) were implanted via an insertion cannula extending 10 mm above the planned target under intraoperative fluoroscopy control and were fixed to the skull. Extension cables and an Activa PC (Medtronic) internal pulse generator (IPG) were implanted.

Post-operative computed tomography (CT) images were acquired at least 6 weeks after surgery for electrode localization to exclude pneumocephalus-related artifacts. Contacts were identified using three-dimensional Euclidean vector calculations after the co-registration of control CT images to T1 anatomical sequences. Active contacts were selected for the study according to proper placement within the ANT, to achieve the most feasible therapeutic effect. The initial programming was postponed for at least 4 weeks after the operation to use the potential micro-lesion effect. The standard starting stimulation-parameters were 5 V, 90 μS, 130 (Center in Budapest)/145 Hz (Center in Pecs), 1 min ON and 5 min OFF cycling mode. Voltage was gradually increased to 7–7.5 V when the standard starting stimulation parameters did not achieve significant seizure reduction. The preoperative (time-point T1) antiepileptic drug regimen was not changed during our study period (after DBS-implantation (time-point T2) and start of stimulation (time-point T3)).

In 17 patients, the activated contacts hit the target (ANT) bilaterally; in seven patients, the activated contact hit the ANT only on the left side; in three patients, only the contact on the right side hit the ANT; and in three other patients, no activated contact was located in the ANT. Supplemental Information 2 presents detailed information about the retrospective (prepared for research purposes) post-operative reconstruction and visualization of the localization of the activated contacts.

Data collection

We retrospectively analyzed 180 ECG epochs selected from the interictal video-EEG–ECG recordings of 30 patients (6 epochs from 3 different video-EEG sessions per patient) Sessions included one epoch while awake and one while in N1 stage sleep; three while awake; and three while sleeping.

During one video-EEG session, patients were continuously monitored using a fully digitalized video-EEG–ECG recording system (Brain-Quick System Evolution, Micromed SpA, Mogliano-Veneto, Italy), where the digitalized video, 21- or 27-channel scalp EEG, and ECG signals were synchronized in time. The monitoring period lasted for at least 2 days. Four ECG electrodes were placed in the anterior and middle axillary lines. We obtained two bipolar ECG leads; the vector of one of the two leads was parallel to the electrical heart axis, while the vector of the other lead crossed the heart axis at an angle of approximately 60–80 degrees. The sampling rate for the EEG–ECG was set to 1024 Hz, which provides the most acceptable resolution for evaluating HRV [32, 46]. The study design is illustrated in Figure 4.

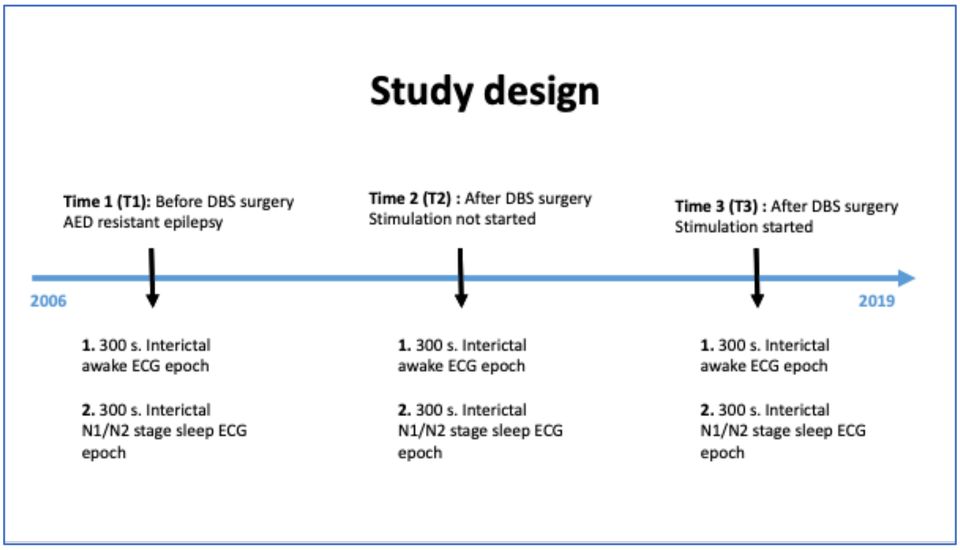


Figure 4. Retrospective study design

Study design: Two interictal epochs (1: Awake, resting and 2: N1- or N2-stage sleep) for each time point (T1–T3) were selected for analysis.

Time 1 (T1): Before the DBS-implantation surgery as part of the presurgical evaluation,

Time 2 (T2): After the implantation surgery but before programming and starting the stimulation,

Time 3 (T3): After the primary programming when DBS was turned on and the stimulation parameters were set.

DBS, deep brain stimulation; N1- or N2-stage sleep, non-rapid eye movement (NREM) sleep

The patients were scheduled to underwent video-EEG sessions for clinical reasons. Altogether, six 300-s (5-min) ECG epochs were selected for each patient. ECG epochs were collected independently at three different time-points (two interictal recordings: one while the patient was awake and alert and resting comfortably, and one during N1- or N2-stage sleep, for each time-point). The first was performed before implantation as part of the presurgical evaluation (T1), the second was after the DBS implantation surgery before programming (T2), and the third was at the time of primary programing and start of DBS therapy (T3). The third session was performed at 2 months after surgery, according to the clinical protocol.

Data analysis

The video-EEG–ECG recordings were reviewed by two investigators who were blinded to the clinical data. Sleep staging was performed by a sleep specialist. Interictal periods were determined by a neurologist who analyzed video-EEG recordings.

Given that seizures are associated with acute changes to HRV, we selected epochs that were: (1) at least 8 hours after the last tonic–clonic seizure; (2) at least 1 hour after the last known clinical (excluding tonic–clonic seizures), subclinical, or electrographic seizure; and (3) at least 1 hour before the next clinical seizure [32].

For evaluation, the ECG data were first reviewed visually to exclude artifacts and non-sinusoidal beats, as proposed by the Task Force of 1996 (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996) [47]. The ECG epochs were analyzed with Kubios Premium HRV Software, using an automatic correction algorithm, as described by Lipponen and Tarvainen, 2019, which provides a robust approach to separate ectopic and misplaced beats from the normal sinus rhythm [48].
The guidelines for HRV measurement from cardiology associations (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996) are not easily generalizable to people with epilepsy. A 24-h Holter monitor does not allow for the accurate evaluation of sleep versus awake HRV, and diurnal variations in HRV may have considerable relevance for people with seizures. Furthermore, HRV over a 24-h period could be increased or decreased considerably by a patient's seizure frequency during that period [49]. Therefore, we followed the standardized minimum protocol for HRV of the International League Against Epilepsy (ILAE) [32], which is more appropriate for patients with epilepsy.

The root mean square of the successive differences (RMSSD) was calculated as the primary outcome measure, following the criteria set by the ILAE for studies evaluating interictal HRV in epilepsy patients:

1. 5-Minute Awake RMSSD: RMSSD was measured over a 5-min period during which the patient was awake, alert, and resting comfortably.
2. 5-Minute Sleep RMSSD: RMSSD was measured over a 5-min period during which the patient was in stage N1 or N2 sleep.
3. Sleep/Awake RMSSD ratio: Sleep RMSSD divided by awake RMSSD.

The standard deviation of RR intervals (SDNN), average heart rate (mean HR; 1/min), and average of RR intervals (mean RR; ms) were also included in the time-domain analysis. The HRV power spectrum was divided into three domains: the high-frequency range (HF: 0.15–0.40 Hz), low-frequency range (LF: 0.04–0.15 Hz), and very low-frequency range (VLF: 0.0033–0.04 Hz). Frequency-domain analysis of HRV was carried out by parametric autoregressive (AR) modelling based methods [50]. We chose these methods, as the AR spectrum yields improved resolution for short samples, and it can be factorized into separate spectral components (Kubios HRV Premium Software; Kubios, Kuopio, Finland).

Additionally, with increasing age, the total power and absolute values of LF and HF power may decrease, which may not be significant for normalized values of LF and HF [51-55]. Therefore, powers of LF and HF bands in normalized units (n.u.) were used to avoid the effect of age on LF and HF power: LF AR normalized units (LF AR n.u. = LF [ms^2] / (total power [ms^2] – VLF [ms^2]) × 100%); HF AR normalized units (HF AR n.u.) = HF [ms^2] / (total power [ms^2] – VLF [ms^2]) × 100, the LF/HF ratio [56-60] and the VLF band logarithmic values (VLF log).

Statistical analysis

For statistical analysis, factorial one-way repeated measures analysis of variance (ANOVA) with post-hoc Bonferroni correction was used (SPSS v 26, IBM Inc, Armonk, NY, USA). One-way repeated measures ANOVA was conducted on the influence of time, as an independent variable, on HRV parameters. We included three time-points (T1: before surgery, T2: after surgery without stimulation, and T3: after surgery after stimulation started). We examined the interaction effects of time and between-subject factors on HRV parameters: responders/non-responders; 2) generalized tonic–clonic (GTC) seizures after surgery; 3) sex; 4) epilepsy duration at the time of surgery (variable set to 1: less than 20 years of epilepsy history, 2: more than 20 years of epilepsy history); 5) side dominance (epileptic foci on the right/left/bilateral); and 6) comorbid conditions (mostly psychiatric or chronic pain, as presented in Table 1). We also retrospectively examined the effect of the localization of electrodes/activated contacts on HRV changes and the effects of age of patients on HRV

We investigated HRV changes in two subgroups: those with bilateral ANT hit of the activated electrodes (17 patients) and those with unilateral or no ANT hit of the activated electrodes (13 patients: 7 left ANT hit, 3 right ANT hit, and 3 no ANT hit).

For statistical analysis, we used $\log_{10}$-transformed values of all HRV parameters.

4. Results

Time-domain parameters

Significant results were obtained for the time-domain RMSSD and SDNN parameters. Time-domain parameters were examined at T1, T2, and T3 for all six ECG epochs. We also reported the ratio of sleep RMSSD/awake RMSSD [32],

Sleep and Awake RMSSD

A repeated-measures ANOVA with Greenhouse–Geisser correction determined that the mean RMSSD for both sleep and awake values at T1 to T3 differed significantly among time points (sleep: $F = 21.117$, awake $F = 27.119$, $p < 0.001$ for both; respectively). See Figure 5.

Post-hoc tests using Bonferroni correction revealed that DBS implantation elicited an increase from presurgical (T1) to post-surgical (T2 and T3) RMSSD values (sleep: T1 mean = 1.294 ± 0.043 vs. T2 mean = 1.562 ± 0.078 vs. T3 mean = 1.789 ± 0.061, respectively) (awake: T1 mean = 1.130 ± 0.047 vs. T2 mean = 1.493 ± 0.088 vs. T3 mean = 1.764 ± 0.041, respectively), which was statistically significant (sleep: $p = 0.038$ for T1 vs. T2 difference and $p < 0.001$ for both T1 vs. T3 and T2 vs. T3 differences; awake: $p = 0.012$ for T1 vs. T2, $p = 0.005$ for T2 vs. T3 and $p < 0.001$ for T1 vs. T3 differences).

RMSSD sleep/RMSSD awake ratio

The effects of time and other factors on the RMSSD sleep/RMSSD awake ratio were not significant ($F = 1.423$, $p = 0.257$ for time), although a trend toward a decreasing ratio from T1 to T2 to T3 was observed.

Mean HR and Mean RR Values

The mean HR and mean RR values did not differ significantly among the T1 to T3 time-points.

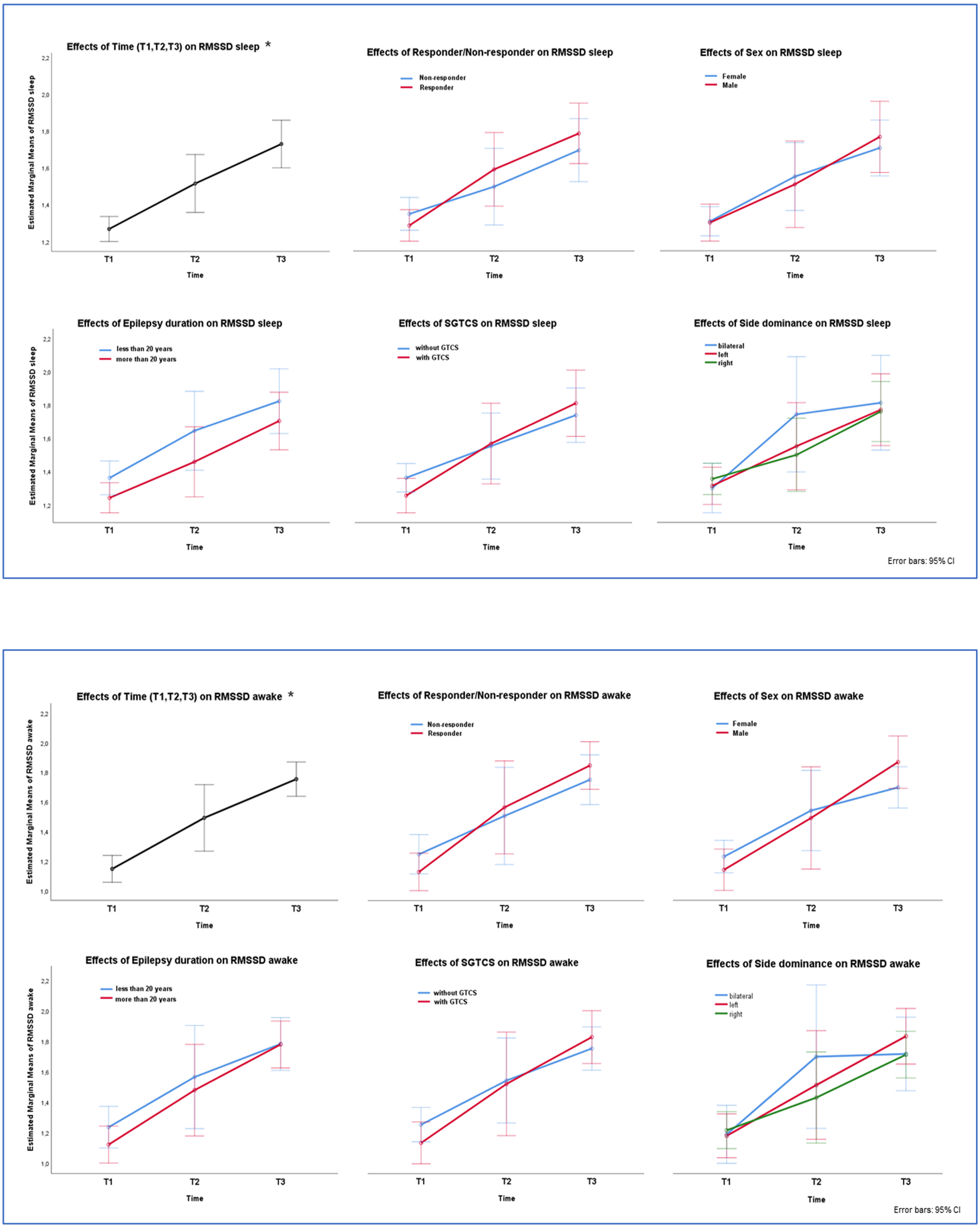


Figure 5. Summary of RMSSD sleep and awake value changes

DBS implantation elicited a significant ($p< 0.05$ indicated with an asterisk) increase in the RMSSD awake values. Responder/non-responder: SGTCS after surgery, sex, epilepsy duration at the time of surgery, side dominance, and comorbid conditions as between-subject factors did not significantly influence the main effects of time (T1–T3).

RMSSD, square root of the mean squared differences between successive RR intervals; SGTCS, secondarily generalized tonic–clonic seizures; DBS, deep brain stimulation.

Between Subject Factors

We observed a significant increase in parasympathetic activity and a decrease in sympathetic HRV components. The between-subject factors did not significantly influence the main effects of time (T1–T3) in either the sleep or awake RMSSD or SDNN evaluations.

However, we found that the effect size was larger in the group of patients with a two-sided ANT hit than in those with a one-sided or no ANT hit. See Figure 6.

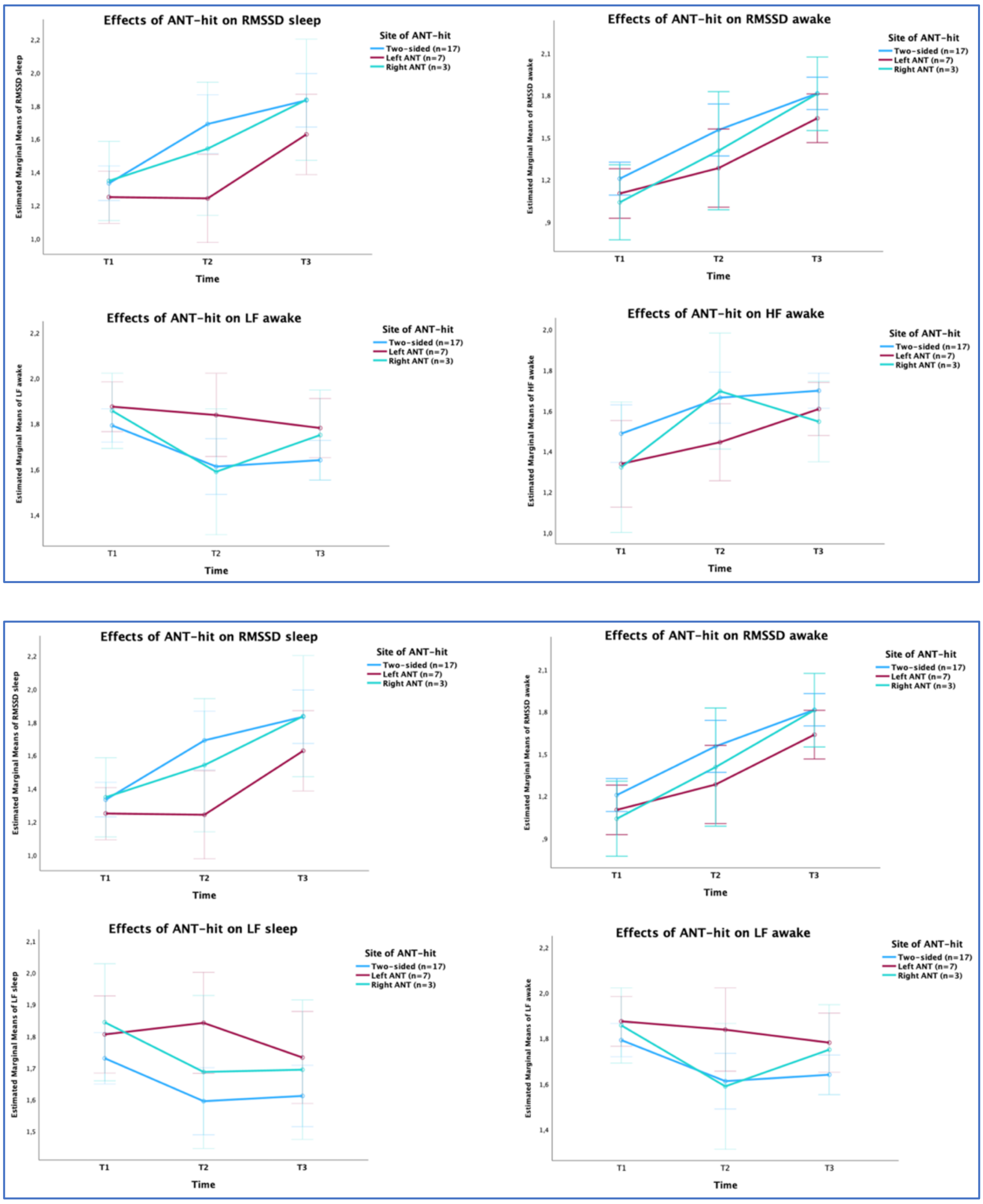


Figure 6. Effects of localization of electrodes (left ANT-hit, right ANT-hit, two-sided ANT hit) on RMSSD, LF, and HF values

No statistically significant effect was found. Patients with two-sided ANT hit tended to have higher RMSSD and HF and lower LF values than did patients with a one-sided ANT hit. Patients with a right-sided ANT hit tended to show higher RMSSD and HF and lower LF values than patients with a left-sided ANT-hit.

When analyzing subgroups (patients with a two-sided ANT hit compared to those with a one-sided or no ANT hit), patients with a two-sided ANT-hit showed a significant increase in sleep RMSSD values after DBS-implantation (T2) but prior to stimulation, while the group of patients with one or no ANT hit showed a significant increase in sleep RMSSD only after stimulation was started.

The RMSSD sleep and awake results were reproducible when examining 60-minute-long epochs.

Frequency-domain analysis

Significant results were found for the frequency-domain parameters of the LF, HF, VLF, and LF/HF awake parameters. Frequency-domain parameters were examined at T1, T2, and T3, with six epochs for each patient.

Sleep and Awake LF

A repeated-measures ANOVA revealed significant effects of time on LF values (sphericity assumed F = 4.797, p = 0.016 for LF AR n.u. sleep and F = 4.737, p = 0.016 for LF AR n.u. awake). Post-hoc tests with Bonferroni correction showed significant decreases between T1 sleep and T3 sleep, between T1 awake and T2 awake, and between T1 awake and T3 awake values.

In subgroup analysis of sleep LF we found that only patients with a two-sided ANT-hit showed significant HRV-changes. When we analyzed 60-minute epochs, we found a statistically non-significant decrease in sleep and awake LF values after DBS implantation and stimulation.

Sleep and Awake HF

When we examined the effects of time on sleep and awake HF AR n.u. values, significant increases were observed in both sleep (sphericity assumed F = 3.385, p = 0.041) and awake (Greenhouse–Geisser correction F = 5.890, p = 0.016) HF AR n.u. values. Post-hoc tests with Bonferroni correction revealed a significant increase between the T1 sleep and T3 sleep values and between the T1 awake and T3 awake values.

In subgroup-analysis, only patients with a two-sided ANT-hit showed a significant increase in sleep HF values after ANT stimulation was started (T3). In the group of patients with one-sided or no ANT hit, no statistically significant change was seen (Table 1).

Awake HF AR n.u. results were reproducible in the group of patients with a two-sided ANT hit (n = 17), when we examined 60-minute video-EEG–ECG epochs.

LF/HF ratio

The effects of time on the sleep LF/HF ratio were not significant (F = 2.445, p = 0.104).

A repeated-measures ANOVA with Greenhouse–Geisser correction (Mauchly's test of sphericity, p = 0.012) determined that the mean awake LF/HF ratio values at T1–T3 differed significantly (F = 8.253, p = 0.005). Post-hoc tests with Bonferroni correction revealed that DBS implantation elicited a decrease from presurgical T1 awake to both post-surgical T2 awake and T3 awake values.

In the subgroup-analysis only patients with two-sided ANT hit showed a statistically significant change in awake LF/HF values after DBS implantation (T1 vs. T2). Patients with a one-sided or no ANT hit showed statistically significant changes only after high-frequency stimulation was started (T1 vs. T3).

The results of the awake LF/HF ratio were not reproducible when analyzing 60-minute-long epochs.

Sleep and Awake VLF AR Log

A repeated-measures ANOVA conducted on the effects of time on the sleep and awake VLF AR log values showed significant changes in VLF values (sphericity assumed F = 10.513 for sleep, F = 11.847 for awake, and p < 0.001 for both sleep and awake VLF). Post-hoc tests with Bonferroni correction revealed that there was a significant increase in VLF between T1 sleep and T3 sleep and between T1 awake and T3 awake values, respectively. The results were reproducible when examining 1-hour-long video-EEG–ECG recordings. The localization of the electrodes (ANT-hit ratio) seemed to influence the effect size in awake VLF and the significance of sleep VLF values.

Between-Subject Factors

The between-subject factors did not show a significant interaction with the main effects of time on the LF, HF, LF/HF awake, and VLF values. However, the hit ratio (two-ANT hit vs. one- or no ANT hit) had a significant effect on the size of post-operative HRV changes.

The location of the electrodes (ANT-hit) seemed to modulate the effect size in awake LF, HF, and VLF recordings. In subgroup analysis of sleep LF, HF, and VLF, we found that only patients with a two-sided ANT-hit showed significant HRV-changes.

A summary of HRV changes is presented in Table 1. The location of ANT-hit (left-sided, right-sided) did not seem to influence HRV significantly. As a tendency, however, patients with a right-sided ANT hit tended to show higher RMSSD and HF and lower LF values than patients with a left-sided ANT hit.

HRV time and frequency domain parameters	N1-N2 Sleep/ Awake	Localization					
		2 contacts in ANT (n=17)			0/1 contact in ANT (n=13)		
RMSSD (ms)	Sleep	T1 <	T2 <	T3	T1 <	-	T3
	Awake	T1 <	T2 <	T3	T1 <	T2 <	T3
LF pow.AR.nu (0.04-0.15 Hz)	Sleep	T1 >	-	T3	-	-	-
	Awake	T1 >	T2	T1 > T3	T1 >	T2	T1 > T3
HF pow.AR.nu (0.15-0.4 Hz)	Sleep	T1 <	-	T3	-	-	-
	Awake	T1 <	-	T3	T1 <	-	T3
LF/HF ratio	Awake	T1 >	T2	T1 > T3	T1 >	-	T3
VLF AR log. (<0.04 Hz)	Sleep	T1 <	-	T3	-	-	-
	Awake	T1 <	-	T3	T1 <	-	T3

Table 1. Summary of statistically significant changes of HRV parameters

Statistically significant changes ($p \leq 0.05$) of HRV-parameters were examined in patients with two-sided ANT-hit and patients with one-sided or no ANT-hit.

Patients with two-sided ANT-hit showed significant HRV-changes in LF sleep, HF sleep and VLF sleep after stimulation was started (T1 vs. T3). In RMSSD sleep in the 2-hit group statistically significant increase of RMSSD sleep and awake was found after DBS implantation (T2) and after stimulation (T3) and statistically significant decrease of LF/HF ratio awake after DBS implantation (T2) and after ANT-stimulation (T3) was started.

Patients with 1or no ANT-hit showed statistically significant change in RMSSD sleep and LF/HF-ratio only after ANT-stimulation was started (T3), no statistically significant change was detectable after DBS implantation (T2). In LF, HF and VLF-sleep no statistically significant change was found in patients with one-or no ANT-hit.

5. Discussion

Main Results

HRV time-domain parameters RMSSD and SDNN, and frequency-domain parameters LF, HF, awake LF/HF, and VLF values changed significantly after DBS surgery and stimulation in both responders and non-responders, reflecting increased parasympathetic tone and suggesting enhanced autonomic stability in patients with drug-resistant epilepsy. This effect was more pronounced in patients with a two-sided ANT hit than in patients with a one-sided or no ANT-hit. Patients with a right-sided ANT-hit tended to show increased RMSSD and HF values and decreased LF values as compared to patients with a left-sided ANT-hit ($p > 0.05$).

Between-Subject Factors

The other factors examined—SGTCS after surgery, sex, epilepsy duration at DBS implantation, side dominance, and comorbid conditions—did not significantly interfere with the effects of DBS implantation or start of stimulation (T2, T3) on most of the HRV parameters, although those with a shorter epilepsy duration, male sex, and response to the therapy tended to have a higher parasympathetic tone. Patients who had epilepsy for less than 20 years had higher RMSSD and HF (parameters reflecting a higher parasympathetic tone) and lower LF values both pre- and post-operatively than those who had a disease duration greater than 20 years ($p > 0.05$). Similarly, higher sleep and awake RMSSD values were recorded in males and responders after the stimulation was started (T3) than in females and non-responders ($p > 0.05$).

The presence of SGTCS before implantation was associated with lower RMSSD values than was the absence of SGTCS; however, interestingly, after the stimulation was started (T3), patients with SGTCS seemed to have greater RMSSD value changes ($p > 0.05$) than did patients without SGTCS. Left- or right-sided epilepsy dominance did not affect HRV values significantly ($p > 0.05$), although we found higher LF and lower HF values in patients with right-sided epileptic foci than in patients with left-sided foci (lower LF and higher HF values), suggesting higher parasympathetic tone in patients with left-sided epileptic foci. Co-morbid conditions did not significantly interfere ($p > 0.05$) with the effects of time (T1, T2, T3). There was a tendency for a decrease in parasympathetic tone in patients with co-morbid conditions as compared to that in patients without co-morbid conditions. In all of the investigated groups, however, an increase in the HRV time-domain parameters RMSSD and SDNN and frequency-domain parameters HF and VLF and a decrease in the frequency-domain parameter LF after surgery were significant ($p < 0.05$) as compared to the presurgical values.

Frequency-domain parameters

We found a significant decrease in awake LF and awake LF/HF ratio values after DBS implantation (T2) and start of stimulation (T3), and a significant decrease in sleep LF after the start of stimulation (T3). We recorded increased HF and VLF values after the start of stimulation under both sleep and awake conditions (T3) (Table 3). These results suggest an increase in parasympathetic tone after the start of stimulation (T3). To elucidate the magnitude of the modulation of the sympathetic nervous system after DBS implantation, further prospective studies will be needed.

Location of the Electrodes: the ANT Hit Ratio

The main influencing factor of effect size and of significant changes in the time- and frequency-domain parameters appeared to be the location of the activated contacts (the ANT hit ratio). We found that patients with bilateral ANT hits had greater increases in parasympathetic HRV parameters than did those with only one or no contacts located in the ANT. The activated contact location or hit ratio seemed to modulate the effect size of the time-domain parameter awake RMSSD and the frequency-domain parameters awake LF, awake HF, and awake VLF. Moreover, in the time-domain parameter sleep RMSSD and frequency-domain parameters sleep HF, sleep LF, and sleep VLF, subgroup analyses showed that only the two-hit group (two activated contacts located in the ANT) showed significant changes post-operatively.

Effects of bilateral vs. unilateral stimulation of ANT on seizure generalization (time to status epilepticus) were examined in previous experimental studies. Hamani et al. reported that bilateral ANT stimulation significantly delayed the time to status epilepticus, whereas unilateral stimulation did not [61]. Examining the autonomic changes of bilateral vs.

unilateral ANT-DBS stimulation, bilateral stimulation seemed to be more effective in influencing HRV than unilateral stimulation.

One-sided stimulation of ANT was also examined. We observed that, among the six responders with a unilateral ANT-hit, five had an activated contact in the ANT on the side that was affected by epilepsy (epilepsy lateralization side). This effect was also observed in an experimental model of focal cortical epilepsy, where ipsilateral lesions in the ANT led to a significant decrease in frequency and duration of seizure generalization [62]. As a tendency, patients with a right-sided ANT hit tended to show higher RMSSD and HF and lower LF values than did patients with a left-sided ANT-hit. These changes were, however, not statistically significant.

Effects of Microlesions on HRV Parameters

Several studies have described [37, 63], that following electrode implantation, a subgroup of patients exhibit a reduction of seizure frequency before stimulation is initiated. This effect is known as the microlesion effect. We examined the effect of DBS insertion (i.e., microlesion) on HRV parameters and observed significant changes (T1 vs. T2) in awake RMSSD and awake LF HRV parameters, suggesting a significant increase in parasympathetic tone after DBS implantation and before the start of stimulation (T2). See Table 1.

This effect seemed to be more pronounced in the two-sided ANT hit group. Furthermore, patients with a two-sided ANT hit showed a significant increase in sleep RMSSD and a decrease in the awake LF/HF ratio values after DBS implantation and before start of stimulation (T2). On the other hand, the group of patients with a one-sided ANT hit showed significant changes only after the start of stimulation (T3).

Changes in Responders and Non-Responders

We found no statistically significant differences when we performed subgroup analysis in responders and non-responders.

As autonomic nervous system structures and control centers are frequently affected by the epileptogenic networks [64], one possible mechanism for the improvement in HRV parameters (modulation of parasympathetic tone) in responders to DBS implantation could be an indirect favorable effect of DBS on autonomic nervous system control and stability. This indirect effect might be due to a decreased seizure number, increased seizure threshold [39], or desynchronized epileptogenic networks [64] in responders.

Another possible mechanism explaining the increase in parasympathetic tone after DBS implantation in both responders and non-responders might be the direct effect of ANT-DBS on autonomic nervous system control centers. The thalamus has widespread cortical and subcortical connections, including those to the anterior insula (AI), which may underlie the processing of information related to gustatory, visceral, and autonomic functions, as well as salient information and emotional processes [65]. The ANT–insula connection was also supported by a topographic connectivity study [66]. As part of the Papez circuit, the ANT receives hypothalamic input via the fornix and mamillothalamic tract, which acts as part of the emotional system of the brain and is involved in memory formation. The relay nucleus projects to the cingulate gyrus, particularly to the dorsal anterior cingulate cortex (dACC) and to the limbic association cortex [67-68]. The ANT is connected to both the main salience network structures (also examined in frontotemporal dementia; [69-70], i.e., the anterior insula and cingulate, and may have a modulating effect on them. Through these connections, ANT stimulation may directly influence autonomic structures. This direct influence might be reflected in improved autonomic stability and increased HRV.

Clinical Significance

We used seizure number as an outcome measure to determine responder/non-responder status, according to the widely accepted clinical follow-up protocol, without considering the severity or diurnal changes of seizures and autonomic nervous system changes after surgery, which are also important factors related to the mental and physical well-being of patients. Drug-resistant epilepsy, increased seizure number, longer disease duration, presence of SGTCS, or bilateral seizure spread [71] suggest unfavorable disease progression and increased mortality. These factors have all been linked to autonomic nervous system changes, including decreased HRV [72] and as potential biomarkers for SUDEP [73].

To gain a more comprehensive outcome estimation after DBS implantation, we suggest including HRV measures in addition to seizure count in the follow-up protocol for evaluating autonomic changes, along with the following factors: seizure severity, presence of bilateral seizure spread or SGTCS, and diurnal changes in seizures. Measuring autonomic stability could effectively facilitate SUDEP risk stratification in patients with epilepsy undergoing DBS surgery and in their post-operative management [73].

Limitations

Due to the retrospective study-design, caffeine/tea/caffeinated soft drinks intake and other individual habits, that might have influenced HRV, could not be monitored. Considering the small number of cases, our study represents preliminary results. Additional prospective studies are required to provide further evidence.

Conclusions

Given the autonomic effects of ANT-DBS, our results suggest that ANT-DBS is a safe treatment option in drug-resistant epilepsy patients who are not candidates for resective epilepsy-surgery [74].

Based on the observation that HRV improved after the surgery, irrespective of the response to DBS status, but seemed to be influenced by the localization of the activated contacts (with better results with a bilateral ANT hit), we suggest that ANT stimulation might have direct neuromodulating effects [75] on autonomic nervous system centers, such as the PAG and salience network, including the dACC and AI. To understand the mechanisms underlying HRV improvement after ANT-DBS implantation, prospective imaging studies are needed to reveal the changes in functional connectivity of the ANT to the autonomic nervous system centers and control structures.

V. Summary of results

We aimed to study the effectiveness of preoperative evaluation, surgical treatment and neuromodulation, postoperative follow-up and rehabilitation examining employement status and quality of life- in a cohort of patients who underwent epilepsy surgery between 2005 and 2016. Further we studied the postoperative outcome of ANT-DBS in patients who underwent neuromodulation in the centers of Budapest and Pecs, examining the effects of ANT-DBS on changes in interictal heart rate variability in patients with drug resistant epilepsy. Below is the summary of our main results.

Sugrical treatment of epilepsy and employment status

- Postoperative outcome of patients who underwent resective surgery in our epilepsy center show a tenedeny similar to international results- 76% of all patients and 78% of patients with temporal lobe epilepsy became seizure-free, proving that effectiveness of epilepsy surgery does not depend on the country or region.
- After resective epilepsy surgery, 54% of the patients were employed, a third of them reported to suffer under discirmination at workplace inidacting that epilepsy continued to be associated with stigmatization and isolation.
- Postoperative seizure outcome is one of the main factors influencing quality of life and employement status. 67% of the patients with Engel Class I were employed, while only 34% in Engel Class II, even less- 20%- in Engel Class III and none of the patients in Engel Class IV.
- Management of patients with epilepsy must include consideration of the psychosocial dimensions of the disorder. Psychosocial treatments should be targeted for development in Hungary and needs to be integrated into the treatment flow of epilepsy centers to provide rehabilitation aiming at reintegration of epilepsy patients in the society.
- Interdisciplinary preoperative work-up, surgery indicated by epilepsy board with participation of epileptologists, neurosurgeons, neuroradiologists, psychiatrists, neuropsychologists and postoperative follow-up with interdisciplinary individualised

psycho-social rehabilitation are gold standars of treating epilepsy and only feasable in interdisciplinary epilepsy centers.

- Postoperative outcome after neuromodulation (VNS, DBS) in epilepsy center at Pecs showed to replicate the tendency of international results proving these treatment options as effective alternativ treatment available in patients not amenable to undergo epilepsy surgery.

Effects of ANT-DBS on changes of interictal heart rate variability

- We examined interictal heart rate variability in patients with refractory epilepsy presurgically, after DBS implantation without starting stimulation and after high frequency ANT-stimulation was started.
- We registered significant increase of heart rate variability in patients after ANT -DBS.
- Based on the observation that HRV improved after the surgery, irrespective of the response to DBS status, but seemed to be influenced by the localization of the activated contacts (with better results with a bilateral ANT hit), we suggest that ANT stimulation might have direct neuromodulating effects on autonomic nervous system centers.
- Given the autonomic effects of ANT-DBS, our results suggest that ANT-DBS is a safe treatment option in drug-resistant epilepsy patients who are not candidates for resective epilepsy-surgery
- Prospective imaging studies are needed to reveal the changes in functional connectivity of the ANT to the autonomic nervous system centers and control structures.

VI. Publications related to this thesis

Citable abstracts related to this thesis

1. Lőrincz KN, Bóné B, Tóth M, Horváth R, Kovács N, Komoly S, Karádi K, Barsi P, Ábrahám H, Seress L, Horváth Z, Dóczi T, Janszky J, Gyimesi C. Epilepsziasebészeti beavatkozások eredményei a Pécsi Epilepszia Centrumban 2005 és 2016 között [**Postoperative outcome of surgical interventions for epilepsy between 2005 and 2016 at the Epilepsy Center of Pécs**]. Orv Hetil. 2019 Feb;160(7):270-278. Hungarian. doi: 10.1556/650.2019.31321. PMID: 30741003.

2. Katalin Lőrincz, Beáta Bóné, Kázmér Karádi, Greta Kis-Jakab, Natália Tóth, László Halász, Loránd Erőss, István Balás, Béla Faludi, Zsófia Jordán, Chadaide Zoltan, Csilla Gyimesi, Dániel Fabó, József Janszky, **Effects of anterior thalamic nucleus DBS on interictal heart rate variability in patients with refractory epilepsy**, Clinical Neurophysiology, 2022, ISSN 1388-2457, https://doi.org/10.1016/j.clinph.2022.11.020.

Coauthored publications

1. Sóki N, Richter Z, Karádi K, Lőrincz K, Horváth R, Gyimesi C, Szekeres-Paraczky C, Horváth Z, Janszky J, Dóczi T, Seress L, Ábrahám H. **Investigation of synapses in the cortical white matter in human temporal lobe epilepsy.** Brain Res. 2022 Mar 15;1779:147787. doi: 10.1016/j.brainres.2022.147787.

2. Tényi D, Tényi T, Csábi G, Jeges S, Bóné B, Lőrincz K, Kovács N, Janszky J. **Increased prevalence of minor physical anomalies in patients with epilepsy.** Sci Rep. 2022 Aug 12;12(1):13707. doi: 10.1038/s41598-022-17853-1. PMID: 35962048; PMCID: PMC9374691.

Presentations and posters related to this thesis

1. Előadás a IV. International Cholnoky Symposium-on, 10-11.05.2018, Előadás címe: Epilepsy- Surgery?, University of Pécs Medical School, 12 Szigeti Street, Pécs

2. Előadás a DGNC-Deutsche Gesellschaft für Neurochirurgie 06-09.06.2021. között megrendezett digitális konferenciáján a „**Veränderungen der Herzfrequenzvariabilität nach Tiefen Hirnstimulation des vorderen Thalamuskerns bei Epilepsiepatienten” témakörben**

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