Masaryk University
Faculty of Medicine

Epilepsy Surgery

Habilitation thesis

(Collection of previously published scholarly works with commentary)

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Brno 2020

Content:

Acknowledgments:

I would like to thank prof. Robert Kuba MD, Ph.D. and prof. Milan Brázdil MD, Ph.D., who taught me both clinical epileptology and research basics. I also want to thank all my clinical collaborators from the First Department of Neurology and from the Department of Neurosurgery at St. Anne's University Hospital. I would like to particularly mention prof. Ivan Rektor MD, Ph.D., Jitka Kočvarová MD, Martin Pail MD, Ph.D., Ondřej Strýček MD, and Klára Štillová MD, Ph.D. from the First Department of Neurology, and assoc. prof. Jan Chrastina MD, PhD., assoc. prof. Eva Brichtová MD, Ph.D., and Jan Hemza MD. Ph.D. et Ph.D. from the Department of Neurosurgery. I would also like to thank my research collaborators Pavel Jurák MSc., Ph.D., Petr Klimeš MSc., Ph.D., Jan Chládek MSc., Jan Cimbalník MSc., Ph.D., and Filip Plešinger MSc., Ph.D. from the Institute of Scientific Instruments, and Pavel Říha MSc. and Martin Kojan MSc. from Masaryk University. Finally, my thanks to my whole family for their lifelong support.

Abstract:

Drug-resistant epilepsy represents a significant health problem. The ideal therapy, with a high probability of complete seizure cessation, is epilepsy surgery with a resection of areas responsible for seizure genesis. Despite numerous studies, resective brain surgery can currently be offered only to some patients for whom it is possible to formulate a rational hypothesis about the location of the epileptic generator. Other patients can be implanted with a neurostimulator.

The habilitation thesis is divided into three main parts. The first part is focused on individual diagnostic steps that are described in more detail. We pay attention to descriptions of magnetic resonance imaging (MRI) and its post-processing, EEG, and invasive EEG (IEEG), clinical semiology, neuropsychology, and positron emission tomography (PET). The last section of this part concerns two relatively common clinical situation: bitemporal epilepsy and MRI-negative temporal lobe epilepsy (TLE).

The second part discusses neurostimulation methods: vagus nerve stimulation (VNS) and deep brain stimulation (DBS). A critical portion of this part is devoted to the development of a predictive algorithm for VNS based on pre-implantation data.

The third part is dedicated to our future research: the evaluation of seizure detectors in real life and the validation of our statistic classifier for predicting neurostimulator efficacy.

Abbreviations

ADHD – attention deficit hyperactivity syndrome, AEDs – antiepileptic drugs, ANT – nucleus anterior thalami, ASL – arterial spin labeling, AT – attenuation of background activity, CT – computed tomography, DBS – deep brain stimulation, BOLD – blood oxygenation level dependent, DKI – diffusional kurtosis imaging, DTI – diffusion tensor imaging, ECG – electrocardiography, EEG– electroencephalography, EMG – electromyography, ETLE – extratemporal lobe epilepsy, FCD – focal cortical dysplasia, FIA – fast ictal activity, fMRI – function magnetic resonance, HD-EEG – high-density EEG, HFOs – high-frequency oscillations, HRV – heart-rate variability, HS – hippocampal sclerosis, IEDs – interictal epileptiform discharges, IEEG – invasive electroencephalography, ILAE – International League Against Epilepsy, MEG – magnetoencephalography, MRI – magnetic resonance imaging, MRR – median of RR interval, NMRR – normalized median of RR interval, PET – positron emission tomography, PNES – psychogenic non-epileptic seizures, PSEs – psychiatric side effects, QoL – quality of life, ReHo – regional homogeneity, RR – RR interval, SANTE – stimulation of the anterior nuclei of thalamus, SIA – slow ictal activity, SPM – statistic parametric mapping, SPM-PET – statistic parametric mapping of positron emission tomography, RNS – responsive neurostimulation, SUDEP – sudden unexpected death in epilepsy, TLE – temporal lobe epilepsy, vHFOs – very high-frequency oscillations, VNS – vagus nerve stimulation, WHO – World Health Organization, 18F-FDG-PET – fluorine-18fluorodeoxyclucose positron emission tomography

Introduction

Epilepsy is a multicausal and often devastating chronic disorder characterized by recurrent spontaneous seizures, affecting around 50 million people worldwide. According to the World Health Organization (WHO), epilepsy is the most common serious neurological condition in Europe and a source of significant long-term disability. It is thought to be directly responsible for about 33,000 deaths in Europe every year, one-third of which could have been avoided if proper standards of care were available. The burden of epilepsy stems from a multitude of issues, including pharmacoresistance (30% of patients) and various comorbidities. This global burden translates into huge socioeconomic costs, estimated at 0.2% of the GDP of developed countries (3 billion euros in the European Union) (Charlson et al., 2016; Neurological Disorders Collaborator Group, 2017; Thakur et al., 2016).

Drug-resistant epilepsy is a major health problem. Currently, the most effective treatment for focal drug-resistant epilepsy is resective surgery. Every year worldwide, thousands of patients with focal drug-resistant epilepsy undergo resective brain surgery to stop their seizures (Engel, 2008). The last 15 years have seen a remarkable evolution in the treatment indications for epilepsy surgery. Notably, the increasing worldwide use of invasive EEG (IEEG) has likely been driven by high numbers of patients referred with extratemporal lobe epilepsies (ETLE) and magnetic resonance imaging (MRI)-negative epilepsies; these categories pose particular challenges for presurgical evaluation (Jehi et al., 2015).

Over the last 50 years, the success rate for surgical interventions in patients with drug-resistant epilepsy has significantly increased. At the moment, it is possible to achieve long-term seizure control in 80% of patients with mesial or neocortical temporal lobe epilepsy (TLE) with

hippocampal sclerosis (HS) or focal cortical dysplasia (FCD) type 2 and for up to two-thirds of patients with ETLE. This achievement is obtained with minimal perioperative risks, which have decreased to approximately 1% (Ryvlin and Rheims, 2016).

Despite this progress in resective surgery and its obvious benefits, surgery has failed to control seizures for a large number of epileptic patients (Krucoff et al., 2017; Téllez-Zenteno et al., 2005). The reasons for these failures are varied, but are thought to be in large part linked to the suboptimal identification of the epileptogenic zone responsible for seizure origin and, consequently, the non-resection or inadequate modulation of the critical nodes and pathways that fundamentally characterize the epileptogenic network (Harroud et al., 2012; McIntosh et al., 2004; Ryvlin and Kahane, 2005; Salanova et al., 2005). Based on these findings, there is still a significant research gap in identifying ideal surgical candidates and optimizing the methods used in the presurgical evaluation.

Despite numerous efforts, many patients with drug-resistant epilepsy are still not indicated for "classical" resective brain surgery. This is attributed to many variables, e.g., epilepsy multifocality, relevant patient co-morbidities, severe mental retardation, personal options, or previous resective surgery failure. These patients can be offered implantation of a neurostimulator: vagus nerve stimulation (VNS), deep brain stimulation (DBS), and responsive neurostimulation (RNS) (Englot et al., 2017). In general, these methods do not offer a high chance for a complete seizure cessation, but they can lead to a significant decrease in seizure frequency, severity, and duration with minimal additional risks (De Herdt et al., 2007; Kuba et al., 2009; Labar, 2004; Renfroe and Wheless, 2002; Vonck et al., 2004).

The basic concept of epilepsy surgery

Epilepsy surgery is related to identifying the epileptogenic zone that is responsible for seizure generation. Complete removal of epileptogenic zone is essential for sustained seizure freedom. Unfortunately, it is not possible to measure the epileptogenic zone directly by any modality. Its borders can be demarcated only indirectly based on the localization of the following areas: (1) epileptogenic lesion, (2) irritative zone, (3) seizure onset zone, (4) symptomatogenic zone, and (5) functional deficit zone (Rosenow and Lüders, 2001). The organization of the epileptogenic network can be simple, well-organized, and easily understandable (Figure 1a). However, some patients have very complex and complicated epileptogenic zone organization (Figure 1b).

Epileptogenic lesion: It is a visible lesion, usually identified by MRI. The epileptogenic lesion can be easily identified and has clear-cut borders. Lesional cases are more likely to become surgical candidates and have more satisfying surgical results. Some patients have no clear MRI lesion; these are called nonlesional.

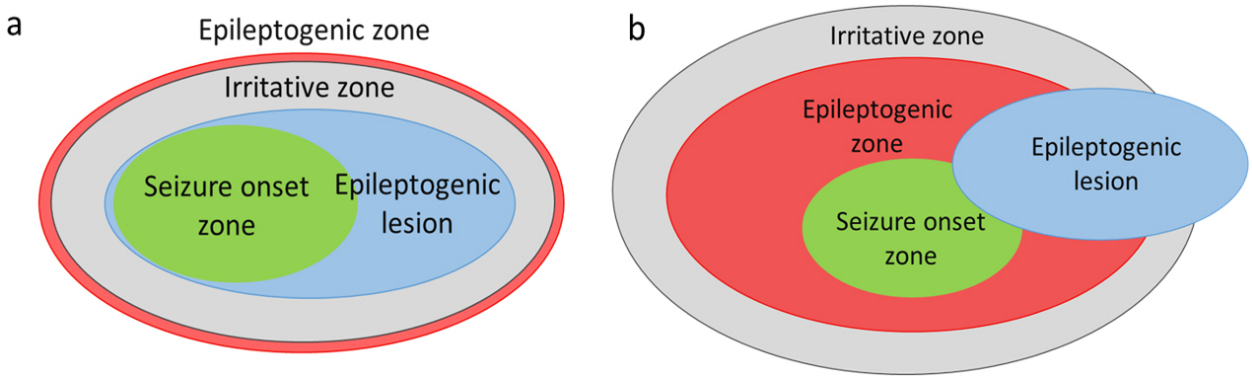


Figure 1: Epileptogenic zone organization

The relation between MRI lesions and the epileptogenic zone is complex. Some visible MRI lesions are not epileptogenic, i.e., they remain "silent" in terms of epilepsy. For this reason, the results of all methods must be evaluated in context. There are limited correlations between the extent of MRI lesions and the borders of the epileptogenic zone. In some cases, partial removal of an epileptogenic lesion is sufficient for complete seizure cessation. In contrast, complete resection can fail to terminate seizures in the others. Two possible theories may explain this observation. According to the first theory, the surrounding tissue is probably responsible for epilepsy. If this surrounding tissue is not removed together with the epileptogenic lesion, epilepsy will persist even after the operation. In the second theory, the failure is conditioned by the limits of neuroimaging, i.e., only "the tip of the iceberg" is visible on MRI and a substantial portion of the epileptogenic lesion remains hidden.

Irritative zone: This zone is responsible for the generation of interictal epileptiform discharges (IEDs).

Seizure onset zone: The seizure onset zone is defined as an area delivering epileptic seizures. This zone can be identified by the results of ictal scalp EEG or IEEG, or by ictal single-photon emission tomography (SPECT) and ictal SPECT co-registered to MRI (SISCOM).

In terms of epilepsy, there are two more zones, the **symptomatogenic zone** and the **functional deficit zone**, for which relations to the epileptogenic zone are even less clear.

Symptomatogenic zone: The symptomatogenic zone is activated by the ictal activity during seizure propagation. The anatomical localization of the epileptogenic zone and the symptomatogenic zone can be remote, which is conditioned by the fact that large parts of the brain

represent functionally silent areas, and ictal signs appear following the activation of the eloquent cortex.

Functional deficit zone: The functional deficit zone is the area of the cortex that is functionally abnormal during the interictal period. This dysfunction may be a direct result of the destructive effect of an epileptogenic lesion or it may be functionally mediated, i.e., caused by abnormal neuronal transmission. The functional deficit zone can be identified by neurological examination, neuropsychological testing, PET, or interictal SPECT.

Epilepsy surgery is a stepwise process in which patients undergo whole batteries of examinations to precisely identify the epileptogenic zone. These batteries can be divided into three levels. The **basic level**, which is compulsory for every patient, usually includes MRI, scalp video EEG, PET, and neuropsychology. Some advanced evaluation should be done in patients in whom a hypothesis about the epileptogenic zone cannot be formulated or is unclear based on the results of the previous examination. This **advanced level** is represented by SISCOM, high-density EEG (HD-EEG) with electrical source imaging (ESI), or some other imaging techniques. **IEEG** represents the third and highest level, which is reserved only for pre-selected patients with a plausible hypothesis about epileptogenic zone localization that requires further confirmation before surgery.

MRI and related methods

MRI is an almost obligatory examination for all patients with epilepsy. Immediately after the first seizure, i.e., in the acute phase, MRI is not required; the performance of standard non-contrasted computed tomography (CT) scans is sufficient to exclude acute brain disorder. However, MRI examinations should be scheduled even in these patients (Bernasconi et al., 2019).

The main goal of MRI is the identification of an epileptogenic lesion; this is essential for further management of patients. For drug-resistant epilepsy, the chances for lesional cases to become seizure-free after surgery are apparently higher than for nonlesional cases (Téllez-Zenteno et al., 2010). The International League Against Epilepsy (ILAE) recommended a standard MRI protocol for epilepsy patients; this protocol includes the use of 3T MRI and involves the following sequences: isotropic, millimetric 3D T1 and FLAIR images, and high-resolution 2D submillimetric T2 images. The MRI should be evaluated by an experienced neuroradiologist and an epileptologist who has access to the patient's further clinical data (Bernasconi et al., 2019).

Despite all efforts, a significant number of patients remain nonlesional. In the past, nonlesional MRI was described in up to 40% of reviewed MRI scans (Bien et al., 2009). We expect this number to be lower now due to technical progress, specifically due to improved MRI quality and the use of a standard protocol for data acquisition.

Our group is focusing on neuroimaging in nonlesional cases. This focus is connected with a grant related to the post-processing of MRI data, functional MRI (fMRI), and tractography, which are evaluated in the context of other clinical data and other results. For this grant, we defined

nonlesional cases as (1) patients without any lesions detected by conventional MRI and (2) patients with some discrete changes that made it impossible to process them directly to the surgery.

We work with the structural and functional MRI techniques detailed below. Additional information is provided by PET, SISCOM, and HD-EEG with ESI; these methods are detailed in individual sections.

Voxel-based morphometry (VBM)

VBM is an automated MRI technique used to study differences in brain morphometry based on changes in the volume or concentration of white and gray matter associated with the presence of FCD or HS. In our research, we focused on the evaluation of T1 voxel-based methods: gray matter volume, gray matter concentration, and junction maps. Junction maps point out the blurring between white and gray matter that is present in FCD (Martin et al., 2017).

fMRI

The function of fMRI is based on the fluctuation in the concentration of oxyhemoglobin and deoxyhemoglobin in the blood (blood oxygenation level dependent [BOLD] signal). IEDs cause alterations in the blood oxygenation that can be transcribed by fMRI. This knowledge led to the development of EEG-fMRI, but its use is complicated by several factors, including the necessity to record EEG during MRI acquisition and the absence of IEDs during a limited time interval. The discovery of spontaneous neuronal activities helped to overcome these limitations. Spontaneous neuronal activities are coherent low-frequency fluctuations in BOLD signals. IEDs modify the amplitudes of these fluctuations; this modification led to the development of amplitude of low-frequency fluctuations (ALF) as an fMRI technique (Zhang et al., 2010).

Another novel method working with fMRI is ReHo (regional homogeneity) which explores the regional coherence of the fMRI time course and is capable of establishing the synchronization of cerebral activity between different brain regions (Zang et al., 2004).

Arterial spin labeling (ASL)

ASL is a method for evaluating cerebral blood flow noninvasively, without the use of any tracer, only by magnetic labeling of blood. In epileptology, it seems that ASL will have comparable value to 18F-FDG-PET or interictal SPECT (Haller et al., 2016).

Diffusion MRI

Epilepsy, like other brain disorders, is a network disease with alterations of connections between brain areas. These alternations of brain connectivity are evaluated by diffusion tensor imaging (DTI) and diffusional kurtosis imaging (DKI), which post-proceed diffusion MRI. DTI works on the macroscopic millimeter scale, which is insufficient for imaging tracks in the areas with high representation (corona radiata, tractus opticus). In these areas, DKI can be useful because of its higher resolution (Lee et al., 2014).

The current aim in our research is to identify individual structural and functional characteristics of individual pathologies and to integrate them in a model individualized to each patient. We anticipate some structural and functional overlap, which will be helpful in the delineation of the epileptogenic zone. This approach is illustrated by the case report of our patient (Figure 2).

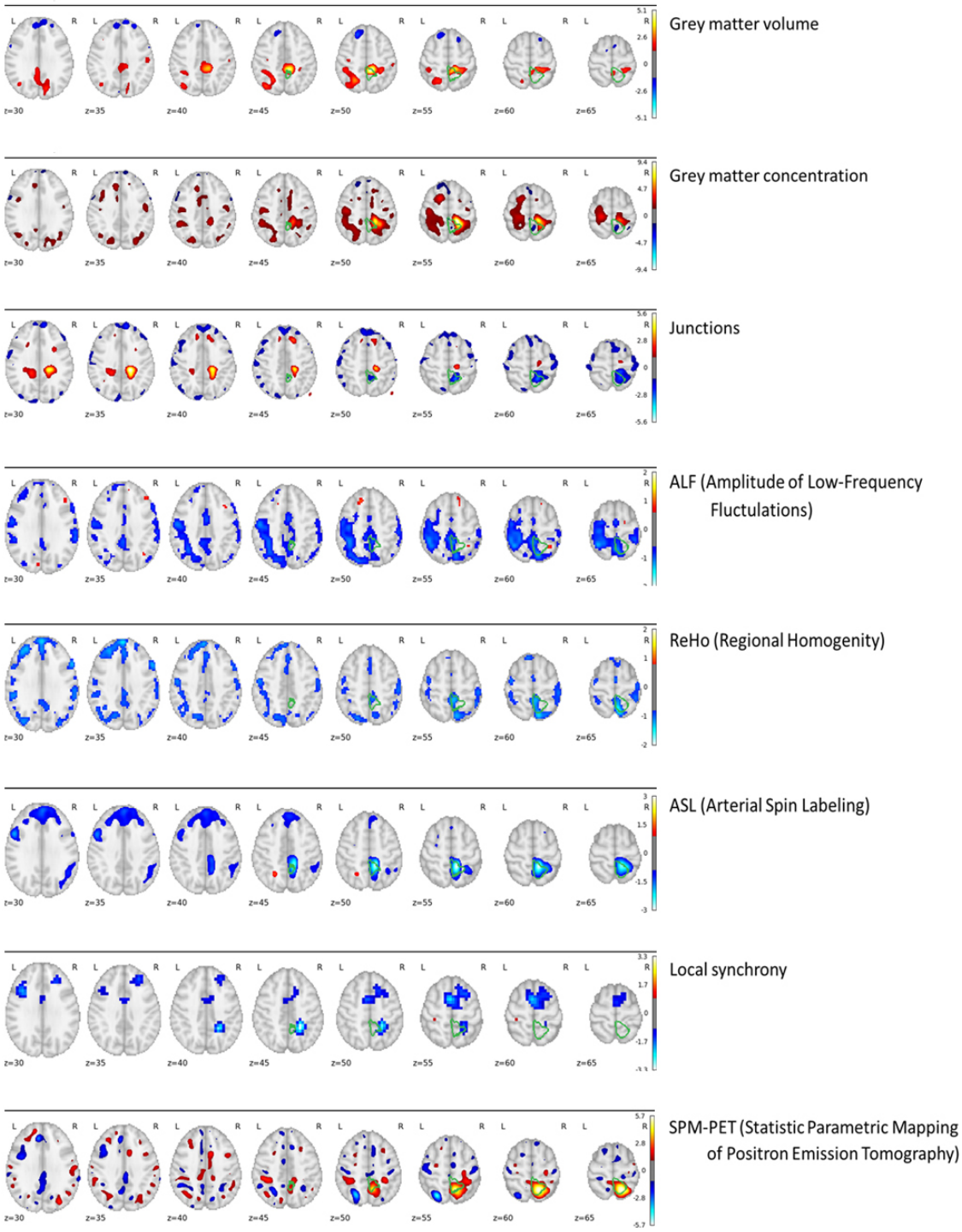


Figure 2: The results of advanced MRI techniques, local synchrony, and positron emission tomography (PET) in a patient

The patient was a 42-year-old female with drug-resistant nonlesional epilepsy. She underwent a resection in the right parieto-occipital region (the boundaries are marked in

green). Advanced MRI techniques show several regions of interest. However, some overlap can be found in the operated area. The correlation between arterial spin labeling (ASL) and statistic parametric mapping of positron emission tomography (SPM-PET) is remarkable in this patient.

Diffusion tensor imaging (DTI) and diffusional kurtosis imaging (DKI) were not done in this case.

EEG and its evaluation

Hans Berger recorded the first scalp EEG in 1924 (Kugler, 1991; Reif et al., 2016). In a short time, EEG was being used for intraoperative monitoring of cerebral activity from the brain surface (Foerster and Altenburger, 1935). In 1949, Robert Hayne and Russell Meyers reported the first attempts at signal recording from deep structures using stereotactically implanted electrodes (Hayne and Meyers, 1950).

EEG provides unique information about cerebral activity; it enables physicians and researchers to map and assess brain functions, connections, and processes in real time on a millisecond scale. From this point of view, EEG cannot be replaced by MRI or by other neuroimaging techniques that can give a detailed high-quality structural perspective.

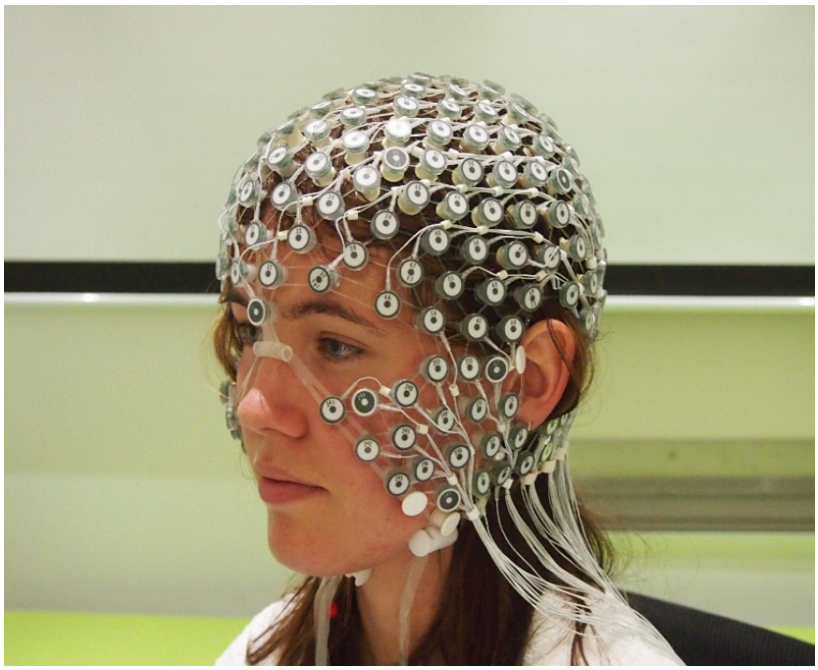


Figure 3: High-density EEG

The essential limitation of standard scalp EEG is its low spatial resolution. HD-EEG with higher numbers of electrodes was initially used to overcome this limitation (Figure 3). The data obtained by high-density EEG requires the determination of their likely generator within the brain, which could be mathematically determined by ESI (Nemtsas et al., 2017). We employed HD-EEG in our project, focusing on neuroimaging of nonlesional epilepsy.

Scalp EEG

Scalp EEG is used in all patients with epilepsy as well as in patients with nonepileptic events. Many authors have worked on the evaluation of scalp EEG and its contribution to decision-making processes or prognostication within epilepsy surgery programs.

We used scalp EEG to analyze the prognostic value of IEDs for patients with TLE associated with HS (HS-TLE) (Doležalová et al., 2014) (Annex 1).

Among patients with TLE, the distribution of IEDs, specifically the lateralization of IEDs between the hemispheres, has prognostic value for surgical outcome. Patients with strictly unilateral IEDs have a better prognosis than patients with blateral IEDs (Chung et al., 1991; Radhakrishnan et al., 1998; Villanueva et al., 2004). This division does not apply for the subgroup of patients with HS-TLE. Three studies analyzing the distribution of IEDs in patients with HS-TLE proved no differences in surgical outcomes between patients with strictly unilateral IEDs and patients with bilateral IEDs (Hardy et al., 2003; Janszky et al., 2005; Krendl et al., 2008). However, some studies found that unilateral IEDs correlate with better surgical outcome (Aull-Watschinger et al., 2008; Schulz et al., 2000).

It was reported that AED reduction does not have any impact on IED frequency or localization, but the influence of AED reduction on IED distribution in terms of lateralization between the two hemispheres was not systematically proven (Gotman and Koffler, 1989; Gotman and Marciani, 1985; Marciani and Gotman, 1986; So and Gotman, 1990; Spencer et al., 1981).

Our study focused on HS-TLE patients. We evaluated: (1) whether there is a change in IED lateralization conditioned by AED reduction, (2) whether there is a change of EEG prognostic value for surgical outcome between periods with full medication and reduced medication.

We retrospectively analyzed the distribution of IEDs between the two hemispheres in patients with HS-TLE. The EEG was analyzed in two periods: full medication (no AED reduction) and reduced medication period (AED dose reduced). We collected 20 minutes of EEG recording in waking and sleeping states in each period (four segments of EEG were collected for each patient). The patients were designated as having unilateral IEDs (more than 90% IEDs on the side with HS) or bilateral IEDs (less than 90% IEDs on the side with HS). The distribution of IEDs was correlated with surgical outcome, defined as excellent (Engel I) or poor (Engel II-IV).

We identified 43 HS-TLE patients. In the full medication period, 38 out of 43 (88%) patients had unilaterall IEDs in the waking state, and 37 (86%) patients had unilaterall IEDs in the sleeping state. In the reduced medication period, the number of patients with unilateral IEDs decreased to 32 (74%) patients in the waking state, and 25 (58%) patients in the sleeping state. We proved a statistically significant change in IED distribution between the full medication and reduced medication periods in the sleeping state ($p=0.003$), but not in the waking state ($p=0.114$).

The lateralization of IEDs had a predictive value for surgical outcome only in the full medication period during the sleeping state (p=0.020). There was a borderline statistical significance of IED distribution to surgical outcome in the full medication period during the waking state (p=0.073). We found no relation between IED distribution and surgical outcome in the reduced medication period in the waking state (p=0.698) or in the sleeping state (p=0.717).

Based on our results, we can summarize that EEG can provide valuable information for surgical outcomes in HS-TLE patients. This information is present exclusively in the period with full medication, i.e., before the initiation of AED reduction. It seems that sleeping EEG is crucial for surgical efficacy prediction. When AEDs are reduced, the EEG predictive value is lost, and there is no clear-cut relation to the surgical results.

IEEG

IEEG is used only in carefully selected patients with drug-resistant epilepsy in the presurgical evaluation. IEEG is used as an "open window" to the brain, enabling the detailed analysis of physiological and pathological phenomena occurring in the brain tissue. Currently, it represents the most accurate method for the characterization of the epileptogenic zone.

Many papers have described the pathological, mainly epileptiform, activity of the brain. This is in contrast with the sparse information about physiological brain rhythms; the majority of such studies were formulated in a pre-MRI period (Gastaut, 1949; Graf et al., 1984; Jasper and Penfield, 1949; Petersen et al., 1953); this could be problematic in interpreting intracerebral recordings as the physiological activity in a given region could be evaluated as pathological and vice versa. Such misinterpretations could have a negative impact on the tailoring of surgery and potentially on surgical results. We tried to overcome this limitation with a common project of intracranial EEG data (Frauscher et al., 2018).

The main aim of this work was to characterize, in detail, physiological awake brain activity in invasive EEG recording (Annex 2).

IEEG data from both intracerebral and subdural electrodes were retrospectively collected in three participating institutes. The "normal" contacts for each patient were selected. These were defined as contacts outside pathological lesion, seizure onset zone, or irritative zone without IEDs or pathological slow waves. All contacts were localized into stereotactic space, and anatomical structures were segmented. Subsequently, the power spectral densities for each anatomical

structure were estimated using Welsch's method. A total of 106 patients, with 1785 contacts, were included in the study. The positions of contacts are shown in Figure 4.

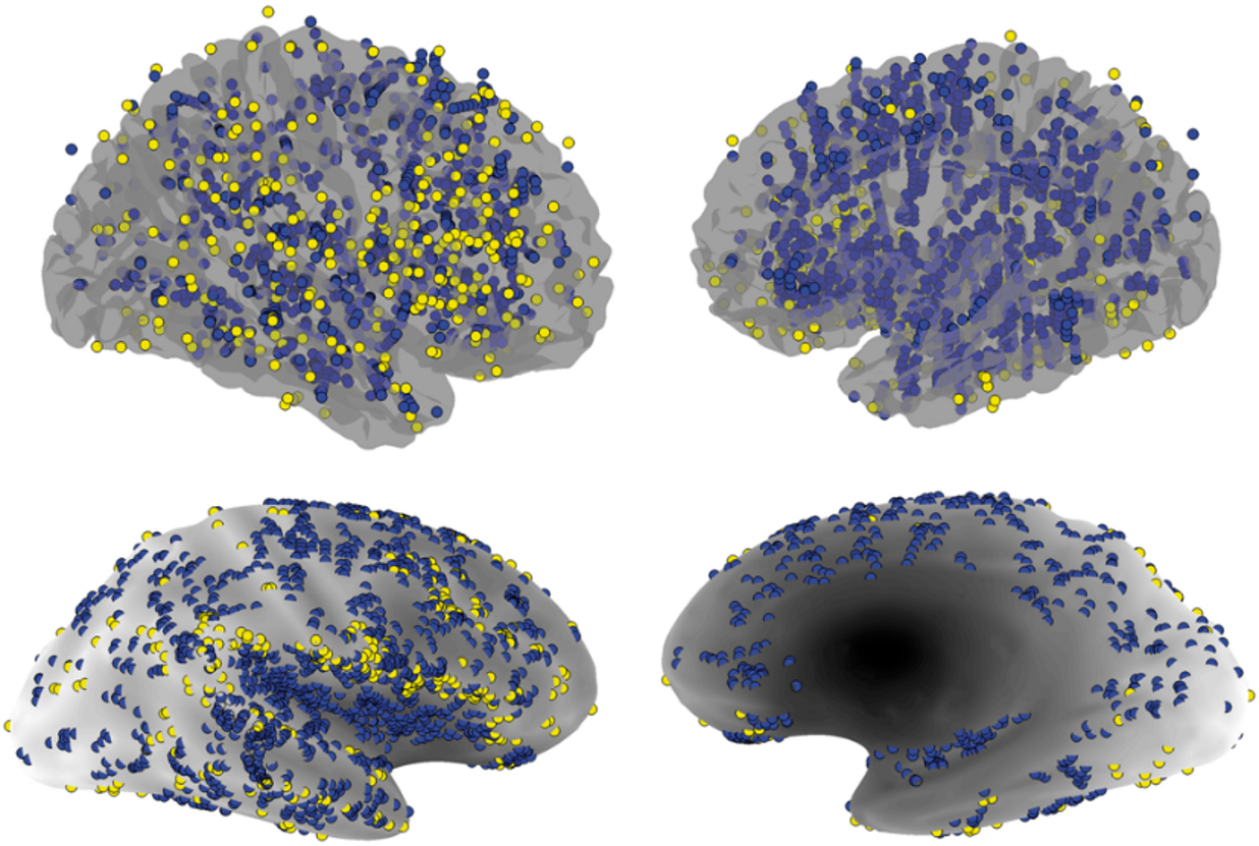


Figure 4: The localization of brain contacts over brain surface
Blue – intracerebral electrodes, yellow – subdural electrodes. Republished with permission.

The individual brain lobes were characterized by different peaks of power spectral density (Figure 5.1). The occipital lobe showed a peak in the alpha band (7.75-10.25 Hz), the frontal lobe in the beta and gamma band (16.75-80 Hz), the parietal lobe in the alpha and beta band (8.75-9.75 Hz, and 16.75-31.75 Hz), and the temporal lobe in the alpha and delta band (7.25-9.25 Hz, and 0.75-2.25 Hz). Some brain regions were characterized by a specific signature (peak present in ≥ 60% of contacts, Figure 5.2). These regions were the precentral gyrus (lateral aspect 20-24 Hz, medial

aspect 24-31 Hz), the opercular part of the inferior frontal gyrus (20-24 Hz), the cuneus (8 Hz), and the hippocampus (1 Hz).

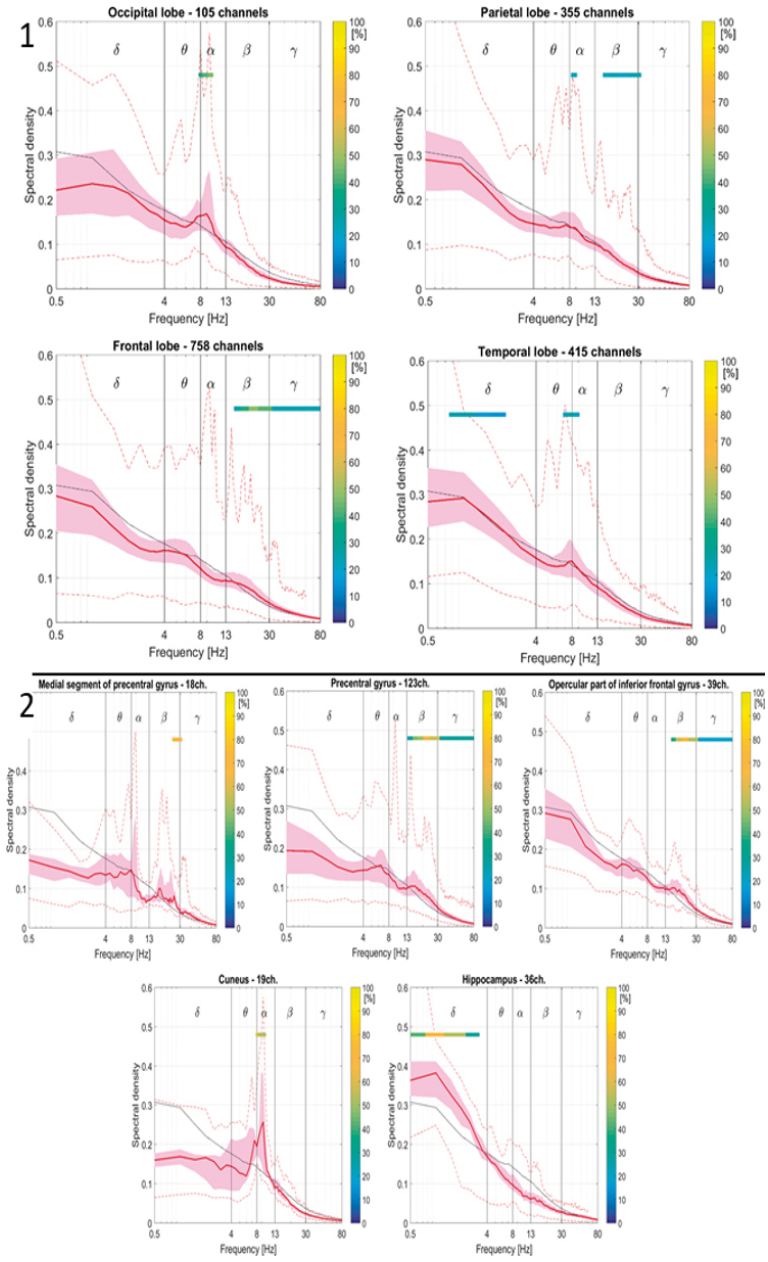


Figure 5: Power spectra in individual brain lobes (5.1) and in regions with a specific signature (5.2) – semi-logarithmic graph

Red line – the median spectral density of all contacts; pink shaded region – the 25th and 75th percentiles; dotted red lines – the upper and lower bound; vertical black lines – the frequency band; colored horizontal segments in the upper part of each graph – the presence of peaks (the color of the line indicates the percentage of contacts with the peak). Republished with permission

This work is the first comprehensive atlas of physiological intracerebral EEG. It could be used in surgery planning and for physiological studies of normal brain activity. We plan to continue to collaborate with the other authors of this study in making a physiological intracranial atlas of sleep stages. The data for this work will be collected prospectively, and our goal is to describe the activity of individual brain regions during sleep.

The changes associated with seizure onsets in intracranial EEG have been systematically studied by many authors because of their significance for our understanding of epileptogenesis (Lee et al., 2000; Spanedda et al., 1997; Spencer et al., 1992). Some patterns were shown to be associated with underlying histopathological changes (Bragin et al., 2009; Williamson et al., 1995); others were associated with the anatomical organization in a given region (Lee et al., 2000; Spencer et al., 1992). It has been proposed that some patterns at ictal onset have different values for the localization of seizure onset. It seems that fast ictal activity at seizure onset is associated with excellent surgical outcomes (Faught et al., 1992; Weinand et al., 1992). The slower frequencies, mainly from the theta range, at seizure onset indicate the propagation of ictal activity and are associated with unsatisfactory results (Schiller et al., 1998).

In one study, we focused on the predictive value of seizure onset patterns in IEEG for surgery in patients with TLE (Doležalová et al., 2013) (Annex 3).

The main aim of this project was to identify whether there is a correlation between the type of seizure pattern present in IEEG in patients with unilateral TLE and surgical outcome, localization of seizure onset zone, or histopathological findings.

We retrospectively identified the patients with TLE who underwent IEEG and subsequent surgery for drug-resistant epilepsy. We analyzed the frequency at seizure onset using the Fast Fourier Transform algorithm. Based on this frequency, patients were subdivided into three groups: (1) fast ictal activity (FIA) – defined by frequency ≥ 8 Hz; (2) slow ictal activity (SIA) – defined by frequency < 8 Hz; and (3) attenuation of background activity (AT) – defined as a diffuse change of EEG signal (decrease in amplitude, increase in frequency) with delayed development of clear-cut rhythmic activity (Figure 6). In the next step, FIA was subdivided into two groups: FIA > 15 Hz and FIA 8-15 Hz. SIA was subdivided similarly into two groups: SIA ≤ 2 Hz and SIA 2 - 8 Hz.

The patients were categorized based on the surgical outcome (Engel I vs. Engel II-IV), on the localization of the seizure onset zone (lateral, mesial, polar), and on the histopathological findings (HS, FCD, negative, or other types).

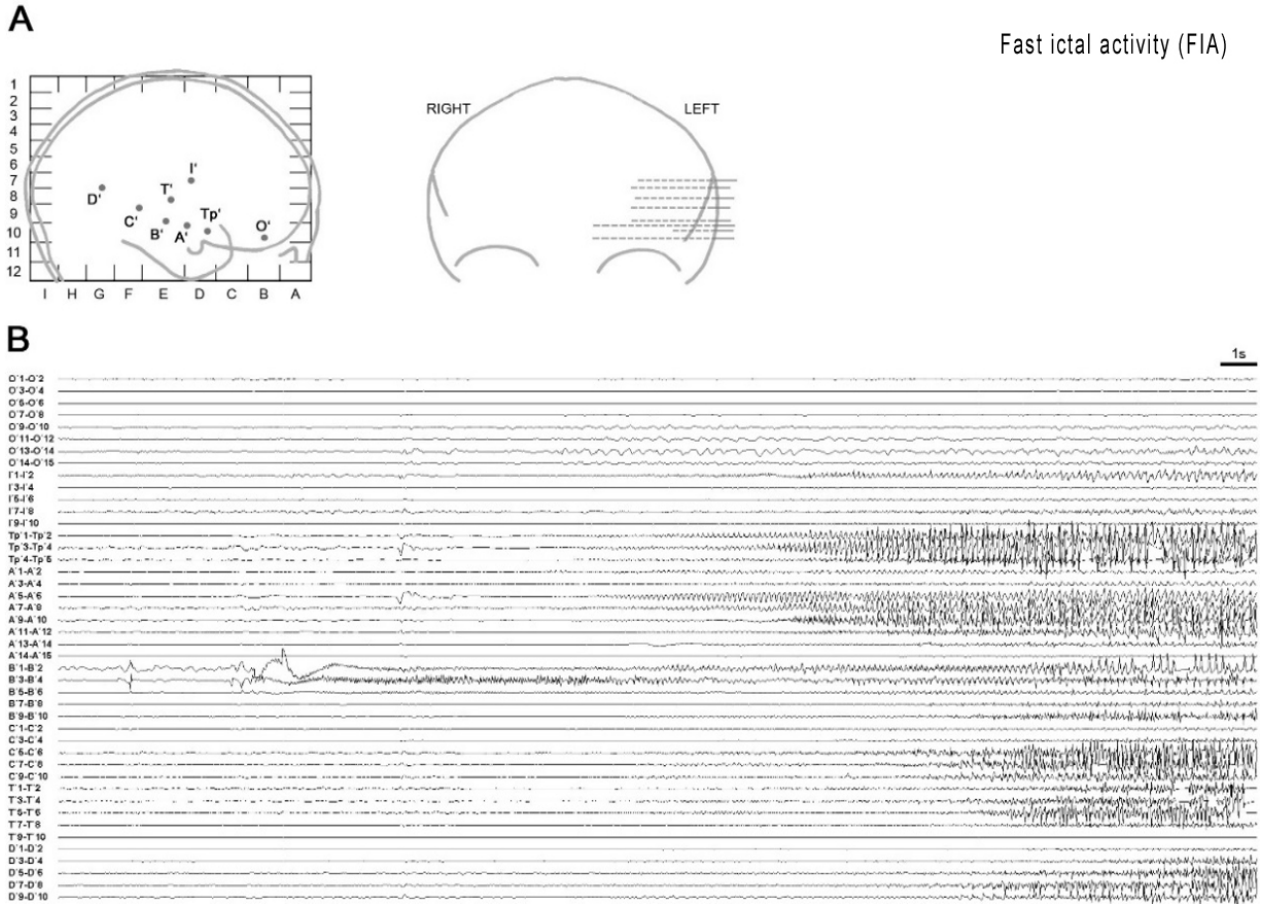
We managed to identify a total of 51 patients: 34 (67%) patients exhibited FIA, 13 (25%) patients exhibited SIA, and 4 (8%) patients exhibited AT. We proved the prognostic value of seizure onset patterns for surgical outcomes. Of the 34 patients with FIA, 29 (85%) had an Engel I outcome, in comparison with 4 (31%) out of 13 with SIA, and 0 (0%) of the 4 with AT ($p<0.001$).

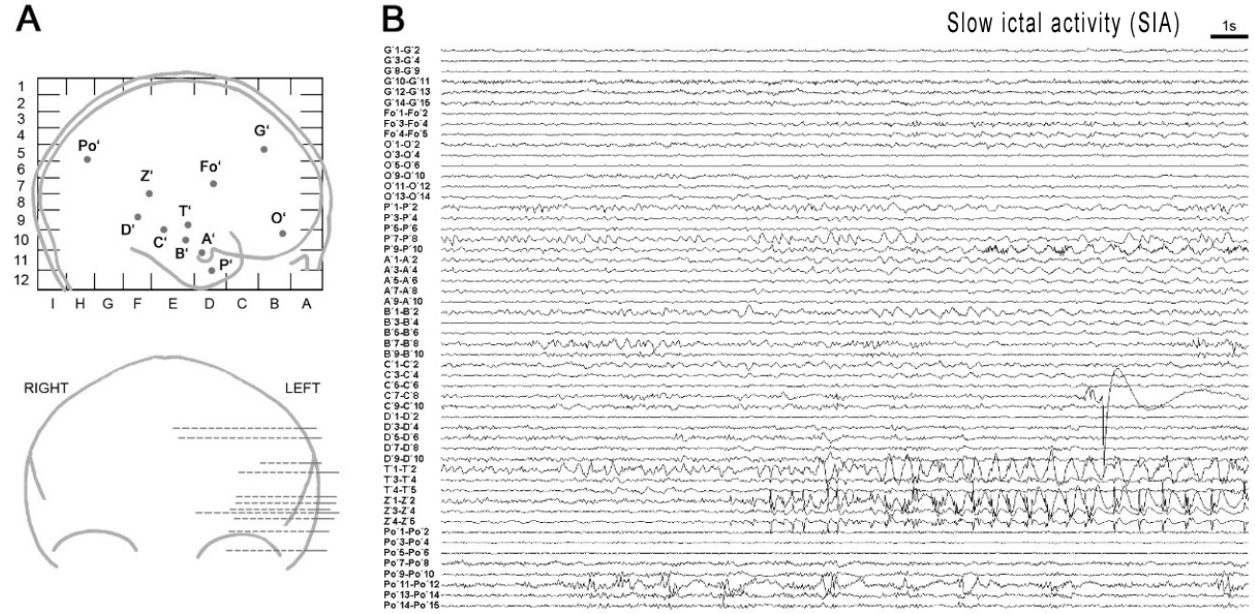
When FIA was subdivided into FIA>15 Hz and FIA 8-15 Hz, we did not find any statistical significance for the surgical outcome ($p=0.164$). When SIA was subdivided into SIA≤2 Hz and SIA

2-8 Hz, we found borderline statistical significance for the surgical outcome (p=0.070); patients with SIA 2-8 Hz tended to have a worse prognosis than patients with SIA≤2 Hz.

We did not find any relationship between seizure onset pattern and localization of seizure onset zone (p=0.878) or between seizure onset patterns and histopathological findings (p=0.362).

Based on our work, we can hypothesize that the seizure onset pattern reflects the relation of the electrode to the localization of the seizure onset zone. If the electrode is directly in the seizure onset zone or in its close neighborhood, it is possible to record fast ictal activity as the first chance of the electrical signal. If the electrode is remote to the seizure onset zone and we record a propagated pattern, the first EEG change is from the slower frequency band.


A
Fast ictal activity (FIA)
RIGHT
LEFT
B
1s


A
B
Slow ictal activity (SIA)
1s
RIGHT
LEFT

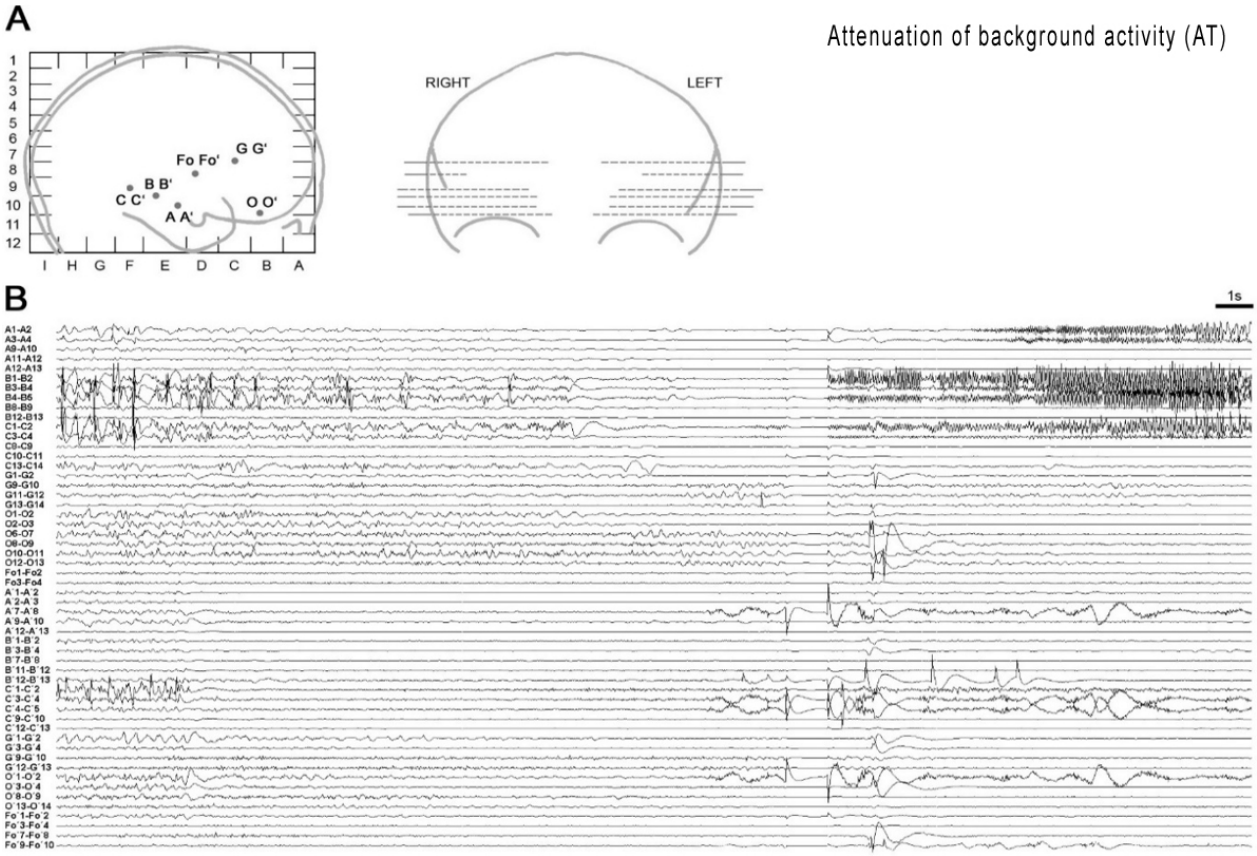


Figure 6: The individual seizure onset patterns in invasive EEG (IEEG)

A – electrode position, B – intracranial EEG

High-frequency oscillations (HFOs)

EEG was traditionally evaluated within Berger's scale, with cutoff values for the highest frequencies of about 50 Hz. A critical change in the conventional clinical and research thinking took place in the early 1990s, when HFOs were described. HFOs were first proven to be present in the hippocampal CA1 region in the rat model (Buzsáki et al., 1992), and subsequently in the area of seizure onset (Allen et al., 1992; Fisher et al., 1992). This started an entirely new era in electrophysiology and clinical epileptology, in which attention was transferred to higher frequencies.

HFOs are the category of brain activity between 80 and 500 Hz, subdivided into ripples (80-250 Hz) and fast ripples (250-500 Hz) (Bragin et al., 1999). In the beginning, HFOs were regarded as the "holy grail" of epilepsy surgery. Several authors showed that resection of areas with high HFO rates is associated with better surgical outcome than resection of areas with low HFO rates (Fujiwara et al., 2012; Haegelen et al., 2013; Jacobs et al., 2009; Usui et al., 2011; van 't Klooster et al., 2011). Importantly, it was shown that the HFO rates present in presurgical electrocorticography do not correlate with surgical outcome, but the HFO rates in postsurgical electrocorticography do correlate, i.e., if there is a high number of remaining HFOs after resection, the patients tend to have worse outcomes (van 't Klooster et al., 2015; van 't Klooster et al., 2017). However, it is not possible to reliably state whether a patient becomes seizure-free in case of HFO high-resection rate (Frauscher et al., 2017). The occurrence of physiological HFOs in several brain regions even complicates the situation (Axmacher et al., 2008; Melani et al., 2013; Nagasawa et al., 2012). Physiological HFOs play an essential role in some processes, such as memory consolidation (Buzsáki et al., 1992; Curio et al., 1997). The frequency of HFOs is not sufficient for clear-cut delineation between physiological and pathological ones (Bragin et al., 2007).

In our study, we tried to determine the existence of other frequency-independent parameters of HFOs, namely rates, duration, and amplitude. This could help differentiate between seizure onset zone, irritative zone, and other areas (Pail et al., 2017) (Annex 4).

The study sample size included 31 patients who underwent IEEG for drug-resistant epilepsy. The HFOs were automatically detected in all these patients and divided into three groups based on their localization: (1) HFOs within the seizure onset zone, (2) HFOs within the irritative zone, and (3) HFOs outside both the seizure onset zone and the irritative zone (the outer zone). The duration and amplitude of HFOs were estimated. Subsequently, the three zones were compared with respect to HFO rates, duration, and amplitude.

The rates of HFOs within the seizure onset zone were significantly higher in the seizure onset zone than in areas outside ($p=0.038$ for ripples, $p=0.018$ for fast ripples). When analyzing the duration of HFOs, the ripples had shorter duration in the seizure onset zone than in the irritative zone and in the outer zone ($p<0.001$). The duration of fast ripples in the seizure onset zone was also shorter in the irritative zone ($p<0.001$) and in the outer zone ($p<0.001$). The amplitude of ripples was higher in the seizure onset zone than in the irritative zone and the outer zone ($p<0.001$). When focusing on fast ripple amplitude, we did not find any differences in amplitude between the three zones.

To conclude, frequency-independent characteristics of HFOs can be helpful in differentiating between physiological and pathological HFOs. The higher rates of both ripples and fast ripples are present in the seizure onset zone. Moreover, both ripples and fast ripples have a shorter duration in the seizure onset zone. The ripples within the seizure onset zone also have a higher amplitude.

Most studies have considered the topic of "classical" HFOs, determined by 500 Hz cut-off value. Descriptions of activities and processes above the 500 Hz limit are rare in the literature and remain beyond the main research stream. Usui et al. (2010) reported the existence of very high-frequency oscillations (vHFOs) defined as the activity above 1000 Hz (Usui et al., 2010). In a later study, they managed to find a correlation between the presence of vHFOs and surgical outcomes in a group of 12 patients with drug-resistant epilepsy (Usui et al., 2015). Our group has also succeeded in describing vHFOs (500-1000 Hz); moreover, we identified a novel electrophysiological biomarker of epilepsy called ultrafast high-frequency oscillations (ufHFOs, 1000-2000 Hz, Figure 7) (Brázdil et al., 2017). These were identified in an interictal state in the hippocampus, amygdala,

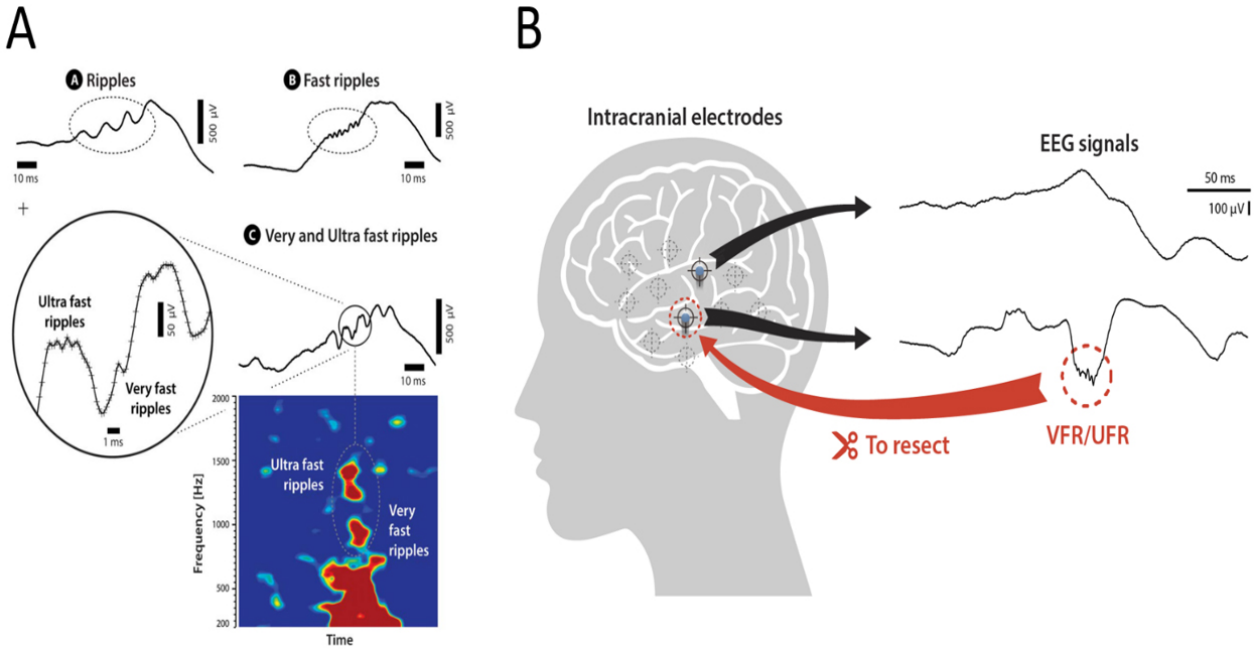


Figure 7: Very fast (500-1000 Hz) and ultrafast (1000-2000 Hz) high-frequency oscillation (vHFOs, ufHFOs)

Examples of different types of oscillations recorded from standard depth macroelectrodes (A) at high frequencies. vHFOs and ufHFOs strongly correlate with positive resection outcome (B). The correlation coefficient was 0.19 in ripples, 0.44 in fast ripples, 0.70 in vHFOs, and 0.90 in ufHFOs.

and entorhinal cortex. Based on the article by Usui et al (2015), we suggest that their group and our group opened an utterly new research field within electrophysiology and epileptology. This field concerns the topic of vHFOs/ufHFOs and their clinical application. We hope we will be able to expand this topic in the near future.

Clinical semiology

The evaluation of clinical semiology is an indisputable part of standard video EEG monitoring. The assessment is essential for both the differentiation between epileptic seizures and nonepileptic events and for the categorization of epilepsy.

Clinical semiology in nonepileptic seizures

The fundamental question is the distinction between psychogenic nonepileptic seizures (PNES) and epilepsy. Certain signs are typical of PNES: long duration, fluctuating course, asynchronous movements, pelvic thrusting, side-to-side head or body movements, forced eye closure, ictal crying, and memory recall (Avbersek and Sisodiya, 2010). PNES and epileptic seizures cannot be reliably distinguished based on tongue biting and urinary incontinence (Brigo et al., 2013). Abrupt onset, ictal eye-opening, and postictal confusion or sleep are highly associated with epileptic seizures (Syed et al., 2011).

The differentiation between other types of nonepileptic attacks and epileptic seizures is less frequent in video EEG monitoring but can be extremely important, even life-saving, in patients with cardiac arrhythmias. The correct diagnosis of syncope can be straightforward in patients with typical signs (sudden loss of consciousness without any additional movements, ECG abnormality). However, the presence of convulsions in “convulsive syncopes” is challenging and leads to misinterpretations. The incidence of convulsive syncope is highly variable in the literature; it ranges from 12% in blood donors experiencing vasovagal syncope to 45% in patients with malignant cardiac arrhythmia (Aminoff et al., 1988; Lin et al., 1982). The movements associated with syncopes are usually described as arrhythmic jerks of the extremities, generalized myoclonus,

and some additional movements (head turns, oral automatisms, and righting movements) (Crompton and Berkovic, 2009).

We described a patient with atypical syncopal manifestation with the most prominent signs of abdominal/thoracoabdominal contractions (Doležalová et al., 2013) (Annex 5).

We published a case report of a 71-year-old female patient who developed attacks of unconsciousness at the age of 70 years. Their frequency was approximately 1 per month in the beginning. The attacks were categorized as epileptic seizures based on motor signs and unremarkable results of an internal examination, including 24-hour ECG. After approximately one year, the frequency dramatically increased to 1 per day. The patient was admitted to our hospital for video EEG monitoring. We recorded several attacks accompanied by asystoles ranging from 20 to 30 seconds. A pacemaker was quickly implanted in the patient.

The attacks were triggered by cardiac asystole; head and eye deviation appeared in the beginning, followed by brief jerks of the upper and lower extremities. However, the most prominent feature was contractions of the abdominal or thoracoabdominal wall. We recorded one attack, in which these abdominal/thoracoabdominal contractions were the only noticeable feature (Figure 8). The patient regained consciousness spontaneously after the restoration of heart activity; it was sometimes accompanied by nausea and vomiting.

The precise mechanism of convulsive movements in syncopes is not fully understood. The most probable hypothesis is that the central pattern generators are responsible for their origin. The central pattern generators are distributed on the subcortical level, mainly the brain stem and spinal cord. They provide the rhythmic behavior, but normally they are inhibited by neocortical control.

They can manifest only in cases of cortical control suppression; this situation leads to the disinhibition of central pattern generators and subsequent rhythmic movements (Tassinari et al., 2009).

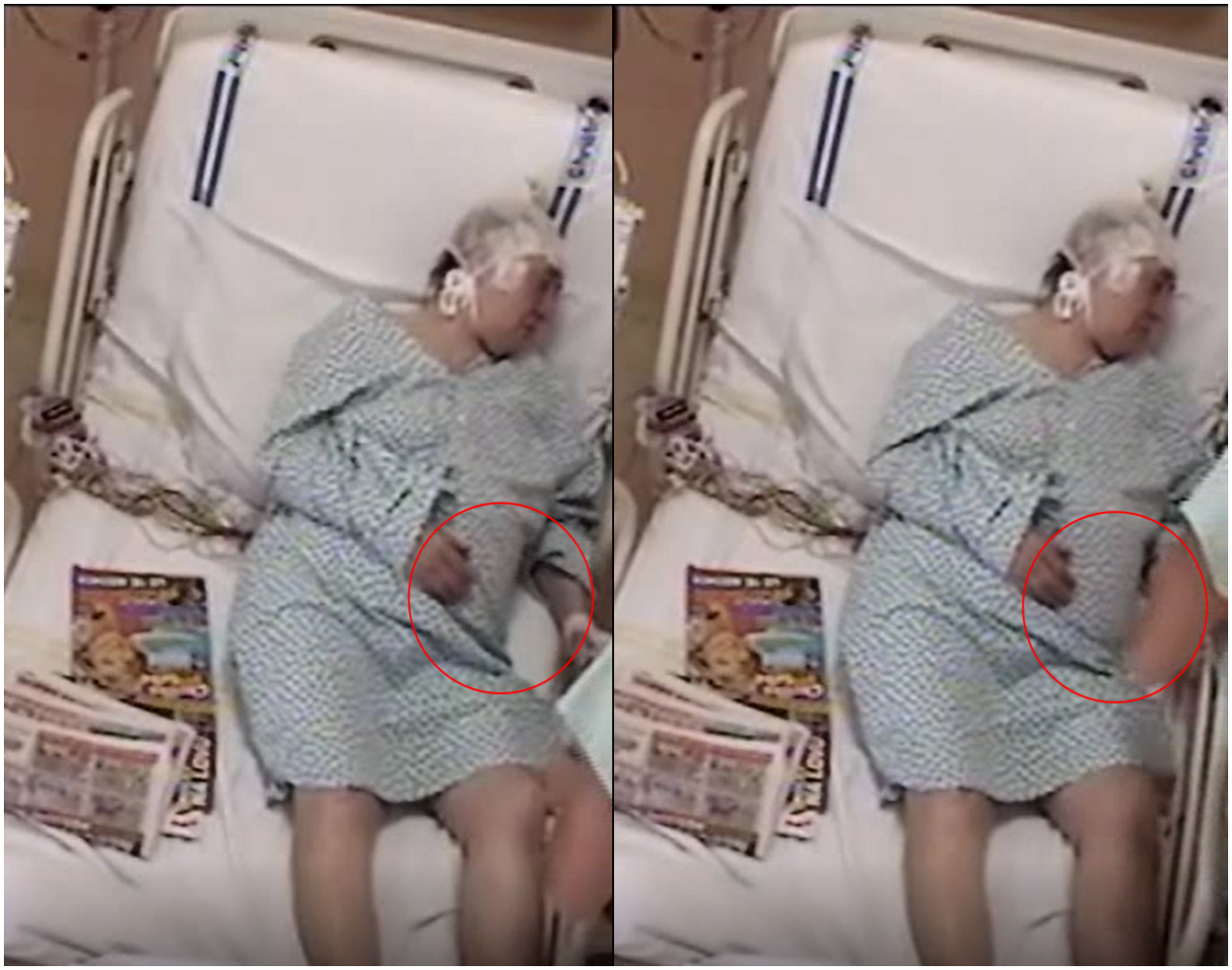


Figure 8: Atypical clinical manifestation of convulsive syncope triggered by heart asystole The most prominent clinical feature was contraction of the abdominal/thoracoabdominal wall. The movements are marked by red circles.

Clinical semiology in epileptic seizures

Seizure semiology is helpful in distinguishing the type of epilepsy (generalized vs. focal, temporal vs. extratemporal). Semiology was described in detail in patients with TLE. Temporal seizures usually have a longer duration and are characterized by a typical sequence of ictal signs. A patient usually reports an aura (epigastric, déjà vu) at the seizure beginning, followed by loss of consciousness. Afterward, patients develop oroalimentary automatisms, hand automatisms, dystonic posturing, and head version with a possible transition to a bilateral tonic-clonic seizure. Some signs have high lateralizing value (e.g., dystonic posture lateralizes seizure onset to the contralateral hemisphere; perseveration of ictal speech lateralizes seizure onset to the non-dominant hemisphere) (Maillard et al., 2004).

Frontal lobe seizures are characterized by shorter duration; the semiology is more diverse than with TLE. However, semiological categorization is possible and correlates with the anatomic organization along the rostrocaudal axis (Bonini et al., 2014).

When differentiating between ETLE and TLE, it necessary to remember “pseudo-temporal” epilepsy. Pseudo-temporal epilepsy is epilepsy with seizures electrophysiologically starting in extratemporal areas but spreading to the temporal lobe, typically with temporal-like semiology (Andermann, 2003). Orbito-frontal, insular, and parieto-occipital, especially posterior cingulate, epilepsies can manifest as pseudo-temporal (Alkawadri et al., 2013; Enatsu et al., 2014; Isnard et al., 2000; Liava et al., 2014; Palmini et al., 1993; Shihabuddin et al., 2001; Williamson et al., 1992). The differentiation in nonlesional cases between temporal and pseudo-temporal epilepsy represents a diagnostic challenge. The distribution of IEDs seems to be helpful. Extratemporal IEDs represent a relevant red flag because they are atypical for pure TLE (Rémi et al., 2011).

We published a case report of a 33-year-old female patient who developed epilepsy at the age of 14 (Annex 6). The patient reported epigastric constriction or gustatory hallucination as an aura. Subsequently, temporal-like seizures developed; early oroalimentary automatisms, upper limb automatisms (mainly left-sided), non-lateralizing nose-wiping, and face-rubbing were present. IEDs were mainly over the left fronto-temporal region, but independent right and left frontal IEDs were also recorded. The ictal pattern slightly differed between individual seizures, but usually the ictal activity appeared over the left anterior fronto-temporal area, then it spread over the left hemisphere and to the contralateral side. MRI was described as normal, with an exception for left-sided thalamic infarct. Neuropsychological testing showed bilateral temporal functional impairment (verbal and visual encoding difficulties). 18F-FDG-PET revealed bitemporal hypometabolism (left-sided involvement was more pronounced).

Based on the inconsistent results of non-invasive investigations, IEEG was suggested as an inevitable further step. An extensive exploration of the temporal areas was performed; the extratemporal regions known for spreading ictal activity to the temporal lobe were also covered, namely the fronto-orbital cortex, insula, and posterior cingulate gyrus. IEDs were independently present in mesial temporal structures and in the posterior cingulate gyrus. The ictal onsets were recorded in all seizures in the posterior cingulate gyrus. The MRI was reviewed, and an inconspicuous change in the gray matter was revealed in the posterior cingulate gyrus in the proximity of the recorded seizure onset. The patient underwent surgery; a limited cortectomy was performed in the left posterior cingulate gyrus (Figure 9). The patient has been seizure-free since surgery.

This case report highlights the problematic differential diagnosis in nonlesional TLE. These patients should be referred for IEEG, which has to cover both temporal and extratemporal areas. This approach has to allow the differential between pseudo-temporal and temporal seizure onset.

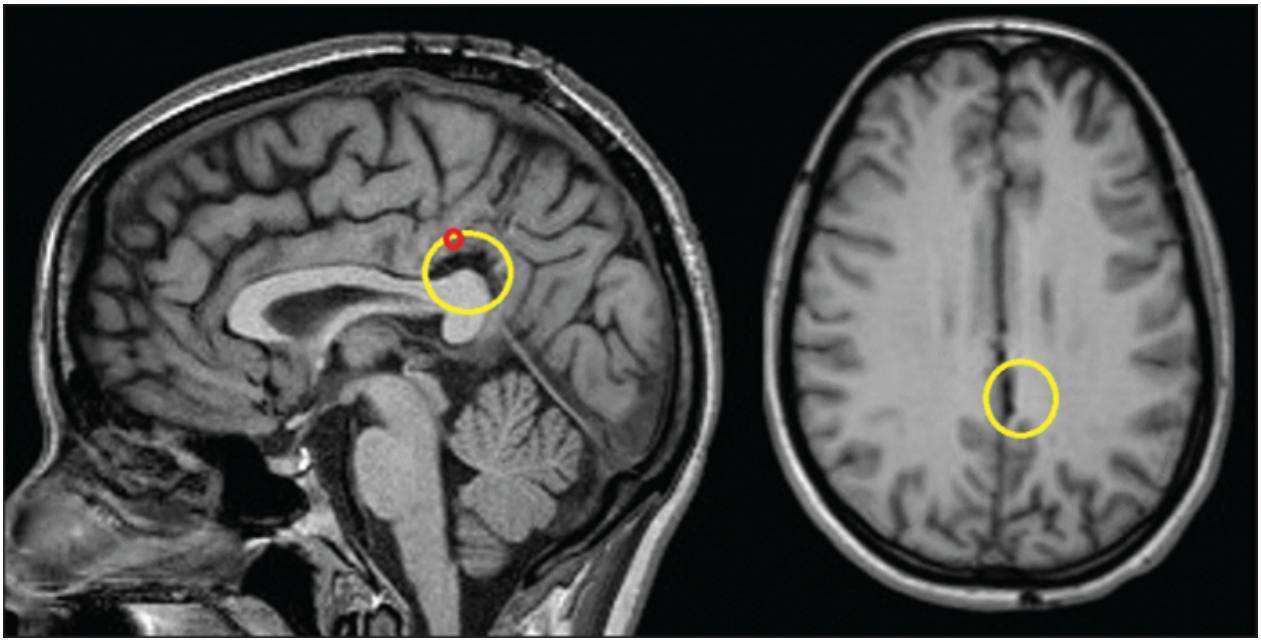


Figure 9: The resection in posterior cingulate gyrus

This figure illustrates the borders of confined resection in the left posterior cingulate gyrus (yellow circle). The red circle represents the area where low-voltage fast ictal activity was recorded.

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Neuropsychology

Neuropsychological testing is a standard procedure within epilepsy surgery programs. Neuropsychological deficits can be conditioned by structural lesions and by the functional derangement of different brain networks (Baxendale et al., 1998; Durwen et al., 1989; Jokeit et al., 2000).

Historically, the most information is available about functional deficits associated with TLE because TLE patients have formed the majority of surgical candidates. TLE affects mainly memory networks. The relation between left-sided TLE with verbal memory impairment is indisputable. The association between right TLE and figural or visuospatial memory is weaker because patients with left-sided TLE also exhibit very often falsely-lateralizing figural or visuospatial memory difficulties (Helmstaedter et al., 1994; Helmstaedter et al., 1995; Loring et al., 1999). TLE patients also have naming difficulties (Malow et al., 1996).

The knowledge about neuropsychological deficits associated with extratemporal epilepsies is less extensive. Patients with frontal lobe epilepsy often have problems with executive functions, working memory, choice of appropriate behavior, the establishment of emotional valences, and evaluating and balancing consequences (Bechara et al., 2000; Rolls, 2000; Sarazin et al., 1998). There is even less information about deficits in insular, parietal, and occipital epilepsies. These "posterior" epilepsies can manifest with aphasia, alexia, agraphia, acalculia, agnosia, or neglect syndrome, but these are not very common and usually well-compensated. They often mimic frontal epilepsies or TLE with their types of dysfunction, depending on the pattern of the spread of ictal activity (Kasowski et al., 2003) .

We know that early-onset epilepsy can alter brain networks and condition the significant redistribution of brain functions. We pursued this topic in our study (Doležalová et al., 2017) (Annex 7).

There are significant differences between the function of the left (dominant) and right (non-dominant) hemispheres. The left hemisphere is responsible for language, verbal, and motor (handedness) function. The clinical variable conditioning this hemispheric shift is the age of insult, i.e., lower age means a higher likelihood of functional reorganization. We know that early-onset epilepsy can condition such a critical shift and cause the redistribution of brain functions. It was demonstrated that left-sided mesial TLE is associated with atypical lateralization of verbal memory and language function (Adcock et al., 2003; Alessio et al., 2013; Powell et al., 2007; Richardson et al., 2003). However, we had no specific information on whether the "pure" temporal lesion as present in mesial TLE is sufficient to cause atypical handedness because of the core function of the frontal lobe for motor functions. In our study, we investigated the occurrence of left-handedness in mesial TLE and clinical variables associated with this left-handedness,

We investigated 73 patients with mesial TLE associated with hippocampal sclerosis. The patients underwent the Edinburgh Handedness Inventory for handedness lateralization. Patients with laterality index from 0 to 100 were categorized as right-handed; patients with laterality index from -100 to 0 were categorized as left-handed.

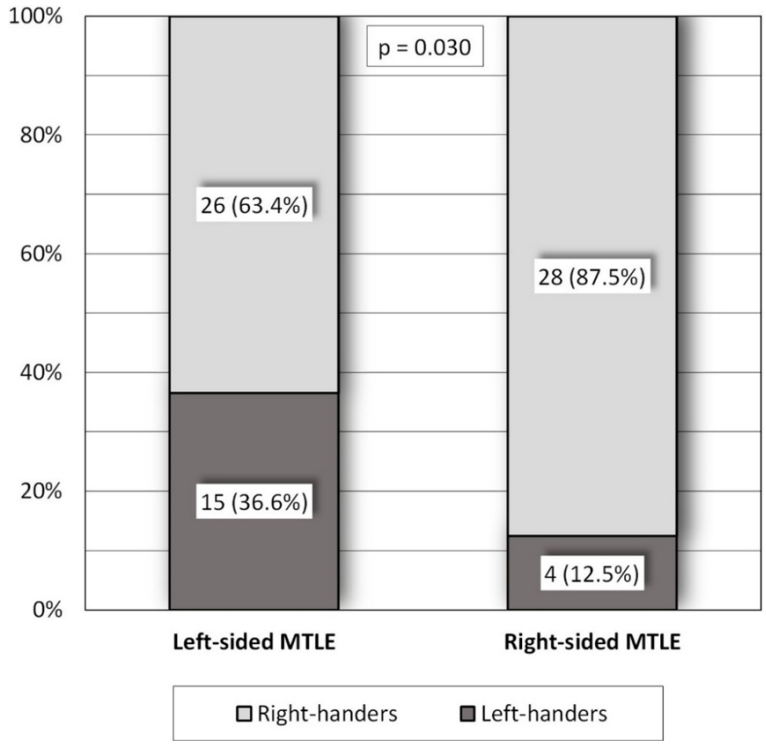

Figure 10: The percent representation of left-handedness and right-handedness in patients with left-sided and right-sided mesial TLE
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There were 32 (43.8%) patients with right-sided mesial TLE and 42 (56.2%) patients with left-sided mesial TLE. Fifty-four (74%) patients were right-handed. The other 19 (26%) patients were left-handed. The representation of left-handed patients was significantly higher among patients with left-sided mesial TLE (p=0.030, Figure 10).

When assessing the clinical variable correlating with the change of handedness in left-sided mesial TLE, we found that left-handed patients had an earlier epilepsy onset (median 8 years of age, min-

max 0.5-17 years) compared to right-handed patients (median 15 years of age, min-max 3-30 years; p<0.001, Figure 11).

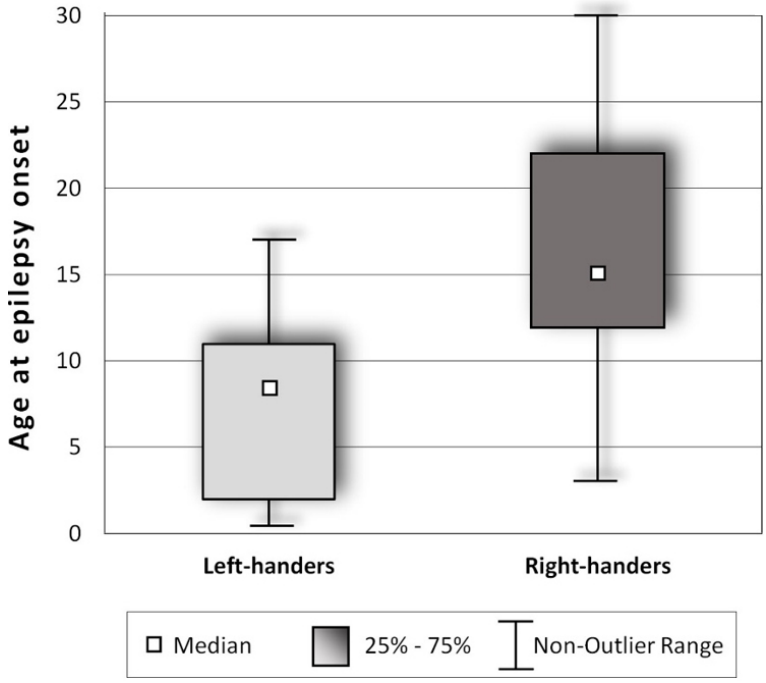

Figure 11: Left-sided mesial TLE - the difference in age at epilepsy onset between left-handed and right-handed patients
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Even a confined lesion like hippocampal sclerosis can alter remote brain function and cause a change of handedness. The probability of this change is age-dependent.

Positron emission tomography (PET)

PET is a functional neuroimaging method that is essential for tailoring surgical procedures. 18F-FDG-PET is routinely performed in an interictal state with a glucose analog. 18F-FDG-PET is an indirect marker of neuronal activity and allows the absolute quantification of cerebral glucose metabolism. Ictal 18F-FDG-PET is not routinely performed because of the short half-life of the tracer.

The seizure onset zone is characterized by a decrease in glucose metabolism in the interictal state. 18F-FDG-PET can be evaluated by both visual (qualitative) and mathematical (quantitative) analysis. Qualitative analysis was found to be reliable in both lateralization of the seizure onset zone and prediction of postoperative outcome in patients with temporal lobe epilepsy (Delbeke et al., 1996; Radtke et al., 1993), but its proper interpretation is influenced by high levels of variability among investigators. To overcome this limitation, methods of mathematical, i.e., quantitative, PET analysis have been developed (Signorini et al., 1999; Takahashi et al., 2012; Van Bogaert et al., 2000).

We tried to establish the benefits of quantitative analysis for epilepsy surgery in our work (Kojan et al., 2018) (Annex 8).

In this work, we compared 18F-FDG-PET using SPM SPM-PET in patients with HS-TLE and control groups in order to assess the differences in the distribution of glucose hypometabolism. In the next step, we tried to identify the differences between HS-TLE subgroups.

We identified a group of 49 HS-TLE patients and 24 control individuals who underwent 18F-FDG-PET. Statistical parametric maps were calculated for each subject. First, SPM-PET was

mathematically compared between patients and controls. Next, we tried to identify the differences in the HS-TLE group in terms of epilepsy duration, HS side, histopathological findings, history of insult, and surgical outcome.

When comparing HS-TLE patients to controls, we found profound bilateral hypometabolism in HS-TLE patients. On the HS side, the hypometabolism was present over both temporal areas (pole,

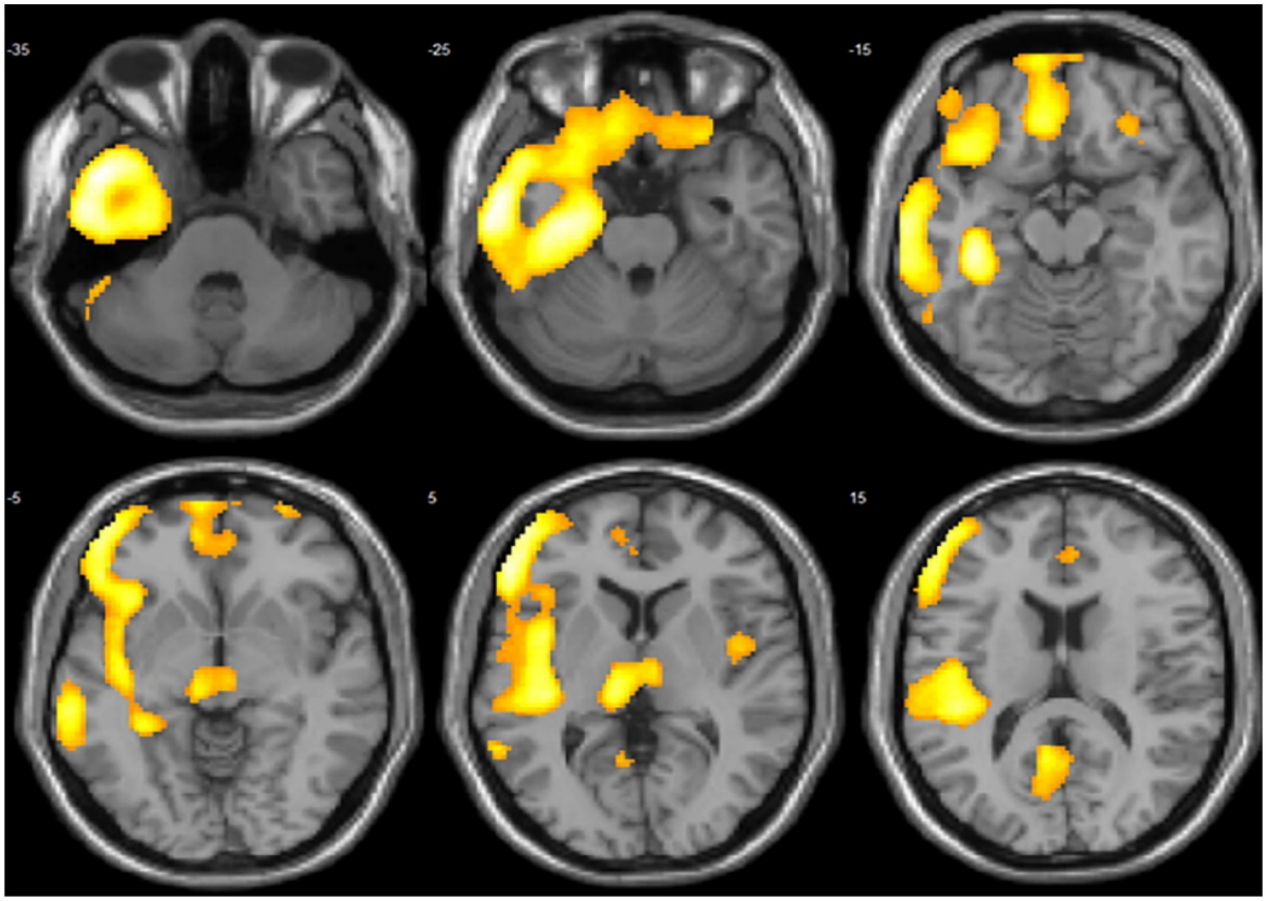

Figure 12: The difference in hypometabolism between patients with temporal lobe epilepsy associated with hippocampal sclerosis (HS-TLE) and a control group using statistic parametric mapping of positron emission tomography (SPM-PET). Republished with permission.

amygdala, hippocampus, parahippocampal gyrus) and extratemporal areas (orbitofrontal cortex, insula, thalamus, posterior cingulate gyrus). On the contralateral side, the hypometabolism was present in the thalamus, anterior cingulate gyrus, and middle cingulate gyrus (Figure 12).

When comparing individual subgroups within HS-TLE, we observed differences between patient subcategories: (1) HS class I and II versus HS class III and IV, (2) excellent surgical outcome (Engel I and II) versus poor surgical outcome (Engel III and IV), and (3) presence versus absence of potential insults (encephalitis, meningitis, febrile seizure). We did not find any significant differences between patients with respect to the HS side and to FCD in the temporal pole.

There are significant differences between HS-TLE patients and controls regarding glucose metabolism. Hypometabolism is bilateral and more widespread on the HS side. There are differences in the hypometabolism distribution even among HS-TLE patients depending on the HS type, surgical outcome, and potential insult.

In general, the sensitivity of 18F-FDG-PET depends on the localization of epileptogenic zone. It is higher for TLE than for ETLE (70-85% for TLE in comparison to 30-60% for ETLE) (Arnold et al., 1996; Drzezga et al., 1999; Juhász et al., 2001; Ryvlin et al., 1998; Won et al., 1999). PET is essential in patients with clinical and electrophysiological characteristics of TLE but without any suspected lesion on MRI. The well-expressed hypometabolism over the temporal lobe could be found in some patients who form MRI-negative, PET-positive TLE groups (Bell et al., 2009; Carne et al., 2004; Carne et al., 2007a; Carne et al., 2007b; Kuba et al., 2011).

Interictal/ictal SPECT and SISCOM

Interictal/ictal SPECT and SISCOM are other functional techniques widely applied within the epilepsy surgery program. They use tracers marked by radioactive technetium (^{99m}Tc-HMPAO) that are applied interictally for interictal SPECT or ictally for ictal SPECT. SISCOM is obtained by mathematical postprocessing of interictal and ictal SPECT; the results are displayed on MRI.

The highest limitation of ictal SPECT is the necessity of applying a radioactive tracer early during the seizure evolution to visualize the seizure onset rather than the propagation of seizure activity to different brain areas (Lee et al., 2006b; Patil et al., 2007). SPECT/SISCOM are mentioned here only briefly because we paid only marginal attention to it.

The decision-making process within epilepsy surgery

Clinicians focusing on epilepsy surgery have to address several questions when managing a patient to find an optimal therapeutical approach. The fundamental problem concerns the localization of the epileptogenic zone. First, a rational hypothesis about its localization and its extent must be formulated. This hypothesis must be based on the results of all the methods used in the presurgical evaluation and on the localization of zones involved in seizure genesis.

There is currently no widely accepted "tool" for precise epileptogenic zone delineation. Some methods for epileptogenic zone characterization have been proposed in the literature, including the epileptogenic index (Bartolomei et al., 2008). The epileptogenic index is a semi-automated method for quantifying the epileptogenicity of different brain areas. This index is based on two variables: (1) the ability of individual brain structures to generate fast discharges, and (2) the time delay between seizure onset and the development of fast discharges in a given structure. A high epileptogenicity index is present in structures that generate fast rhythms early in the onset, meaning that the structure is highly epileptogenic. The epileptogenic index has been used in several studies, but there are doubts about its usefulness (Aubert et al., 2009; Neal et al., 2020; Pizzo et al., 2017).

In our research, we focused on two clinically relevant situations: MRI-negative TLE epilepsy (Doležalová et al., 2016a) (Annex 9), and bitemporal epilepsy (Řehulka et al., 2014) (Annex 10).

Clinical situation: MRI-negative TLE – differences between mesial and neocortical types

In MRI-negative TLE patients, it is essential to differentiate between those with mesial seizure onsets and those with neocortical seizure onsets for precise seizure tailoring and minimization of adverse events. In most cases, the differentiation can be made based on chronic intracerebral recording. We tried to delineate these two groups, i.e., mesial and neocortical MRI-negative TLE, based on a non-invasive analysis.

Our retrospective study included a total of 20 patients with MRI-negative TLE who underwent intracerebral recording before surgery. According to the localization of the seizure onset zone in IEEG, the patients were subdivided into mesial (amygdala, hippocampus, parahippocampal gyrus) and neocortical MRI-negative TLE groups. We tried to find differences between the following variables: demographic data, FDG-PET findings, interictal and ictal semi-invasive EEG, seizure semiology, results of surgery, and histopathological findings.

Within 20 MRI-negative TLE patients, 13 (65%) patients had mesial seizure onset zones and 7 (35%) patients had neocortical seizure onset zones. The statistically significant differences between mesial and neocortical MRI-negative TLE patients were present in the IED distribution (neocortical MRI-negative TLE patients exhibit extratemporal IEDs more often, $p=0.031$) and seizure lateralization (all neocortical MRI-negative TLE patients had at least one non-lateralized or falsely lateralized seizure, $p=0.044$). When analyzing seizure semiology, we managed to identify some trends, but a statistical comparison was not possible because of the low numbers in each group. No differences were found between other variables.

In conclusion, two-thirds of patients with MRI-negative TLE have mesial seizure onset zones and one-third of patients with MRI-negative TLE have neocortical seizure onset zones. Differentiation based on non-invasive data is challenging despite some distinctions in IED distribution and seizure lateralization. However, the surgical results are satisfactory in both groups, comparable to MRI-positive TLE cases.

Clinical situation: Bitemporal epilepsy

Our next study focused on the analysis of bitemporal epilepsy (Řehulka et al., 2014) (Annex 8). First, it is necessary to clarify the definition of bitemporal epilepsy. The definition differs substantially among publications. In some publications, the definition of bitemporal is based on independent seizures arising from both temporal lobes in scalp EEG (Holmes et al., 2003). Some authors have used various combinations of different criteria (scalp or sphenoidal EEG, MRI, and neuropsychological) (Spanedda et al., 1997). We adapted the definition of Hirsh et al. (1991), who defined bitemporal epilepsy as independent seizures originating from both temporal lobes based on IEEG analysis (Hirsch et al., 1991). We also included patients in whom habitual seizures were recorded from one temporal lobe and elicited by electrical stimulation from the contralateral side. In our study, we tried to characterize the bitemporal group in more detail and to establish differences when comparing to strictly unitemporal ones.

We retrospectively identified a group of patients with bitemporal epilepsy; these patients were matched to the patients with unilateral temporal lobe epilepsy. We then compared bitemporal and unitemporal patients in terms of demographic data, scalp EEG findings, and ictal semiology. From the electrophysiological point of view, we evaluated the presence or the absence of early rhythmic theta/delta activity, time to development of rhythmic theta/alpha activity, bitemporal propagation

time, and ictal activity duration. We evaluated the presence of ictal signs: early oroalimentary automatisms, ictal motor signs (early nonversive head-turning, lateralized ictal immobility of the upper limb, ictal dystonia, rhythmic ictal nonclonic hand motions [RINCH], peri-ictal vegetative symptoms (retching with/without vomiting, cough, urinary urge, and water drinking), peri-ictal motor signs (peri-ictal nose-wiping, peri-ictal bed leaving), and duration of peri-ictal unresponsiveness (short ≤ 3 min, medium 3-5 min, long > 5 min), defined as the period from the end of EEG ictal activity to the restitution of both fluent speech and orientation.

We found statistically significant differences between bitemporal and unitemporal epilepsy when analyzing seizure semiology in the presence of ictal motor signs and the duration of postictal unresponsiveness. At least one ictal motor sign was observed in 18 (20.7%) out of 87 seizures in bitemporal epilepsy vs. in 47 (61%) out of 77 seizures in unitemporal epilepsy ($p<0.001$). Patients with bitemporal epilepsy tend to have a longer duration of postictal unresponsiveness ($p=0.002$). Patients with bitemporal epilepsy had postictal unresponsiveness < 3 min in 18 (28.6%) seizures and > 5 min in 27 (42.9%) out of 63 seizures; patients with unitemporal epilepsy had postictal unresponsiveness < 3 min in 34 (57.6%) and > 5 min in 11 (18.6%) out of 59 seizures. No other statistically significant differences were found when analyzing other variables.

In our study, we managed to demonstrate differences in ictal semiology between patients with unitemporal and bitemporal epilepsy. Patients with bitemporal epilepsy have poorer ictal semiology in terms of ictal motor signs and need a longer time to reach complete recovery.

Neurostimulation methods

In patients who could not be offered "classical" resective surgery or in whom epilepsy surgery failed to abolish seizures, neurostimulation methods represent a possible therapeutic option. Although complete seizure cessation after implantation is relatively rare, neurostimulation can bring significant seizure reduction and improvement of QOL (Fisher et al., 2010; Harroud et al., 2012; Ma and Rao, 2018; McIntosh et al., 2004; Orosz et al., 2014; Ryvlin et al., 2014; Ryvlin and Kahane, 2005; Salanova et al., 2005).

The efficacy can be measured by average seizure reduction or responder rate. The responder rate is traditionally defined as a percentage representation of patients with at least 50% seizure reduction (≥50% seizure reduction). The responder rate of all neurostimulation methods is approximately 50% in the first year after implantation with subsequent increases (Fisher et al., 2010; Harroud et al., 2012; Ma and Rao, 2018; McIntosh et al., 2004; Orosz et al., 2014; Ryvlin et al., 2014; Ryvlin and Kahane, 2005; Salanova et al., 2005).

At the moment, three neurostimulators are approved for the treatment of drug-resistant epilepsy: (1) VNS, (2) DBS, and (3) RNS (not approved in Europe).

The precise antiepileptic mechanism of neurostimulation methods is not fully understood. It is based on the historical observation that the modulation of some cortical or subcortical structures can influence brain excitability and subsequently lead to seizure reduction. The following structures were chosen as possible stimulation targets: cerebellum, caudate nucleus, thalamus (centromedian, anterior, subthalamic nuclei), vagus nerve, and the cortical area of the seizure onset itself (Theodore and Fisher, 2004).

The first attempts with neurostimulation in the treatment of drug-resistant epilepsy were made with the cerebellum (Cooper et al., 1973; Reimer et al., 1967). Despite the promising results of preliminary and uncontrolled studies, the outcomes of a controlled randomized study were disappointing (Davis and Emmonds, 1992; Van Buren et al., 1978; Wright et al., 1984). The efficacy of cerebellar stimulation was not proven. Despite the apparent limitations, specifically the small patient sample (only 12 patients were included), the idea of cerebellar stimulation in the treatment of epilepsy treatment was abandoned and attention was focused on the identification of novel targets. In 1990, preliminary results with stimulation of the vagus nerve were introduced (Penry and Dean, 1990; Uthman et al., 1990; Uthman et al., 1993). The efficacy and safety of this method were subsequently proven (Ben-Menachem et al., 1994; Handforth et al., 1998), and VNS became the first authorized neurostimulation system for the treatment of drug-resistant epilepsy.

Vagus nerve stimulation (VNS)

VNS is the most widespread neurostimulation method for the treatment of drug-resistant epilepsy; it has been implanted in over 100,000 people, a third of which are children, around the world (Ben-Menachem, 2002; Englot et al., 2017).

VNS was approved for the treatment of drug-resistant focal epilepsy based on the results of two randomized, double-blind controlled trials, EO3 (multicenter international) and EO5 (multicenter USA) (Ben-Menachem et al., 1994; Handforth et al., 1998). These studies compared the efficacy and safety of high-level stimulation (therapeutic; the stimulation frequency ranged between 20 and 50 Hz) and low-level stimulation (sham; the stimulation frequency was 1 or 2 Hz). The mean reduction in seizure frequency in EO3 was 24.5% for active (high-frequency) stimulation and 6.1% for sham (low-frequency) stimulation; in EO5 it was 24.5% for active stimulation and 15% for sham stimulation (Ben-Menachem et al., 1994; Handforth et al., 1998).

VNS efficacy

Further studies focused on the long-term effect of VNS; they proved an increase in VNS effectiveness over time. Révész et al. (2018) observed 130 consecutive patients with epilepsy. They found significant seizure reduction; the responder rate increased from 22.1% in the first year to 43.8% in the fifth year regardless of changes in AEDs (Révész et al., 2018). However, there is still limited information about patient responses to VNS with more than a 10-year perspective (Elliott et al., 2011; Révész et al., 2018; Serdaroglu et al., 2016).

We tried to address this limitation in our study (Chrastina et al., 2018b) (Annex 11).

The main aim of this study was to evaluate our long-term (10-17 years) experience with VNS in a group of drug-resistant epilepsy patients. The second aim of this study was to find the predictors for long-term VNS response based on clinical data analysis.

We retrospectively analyzed the response to VNS in patients who were implanted at least 10 years ago. Based on this response, patients were categorized as follows: non-responder (seizure reduction < 50%), responder (seizure reduction ≥ 50%), and 90% responders (reduction ≥ 90%).

We found 74 patients who were implanted with VNS for at least 10 years; their response to VNS is summarized in Figure 13. The responders' rates were as follows: 38.4% in year 1, 51.4% in year 2, 63.6% in year 10, and 77.8% in year 17. The 90% responders' rates were: 1.4% in year 1, 5.6% in year 2, 15.1% in year 10, and 11.1% in year 17. Changes were made in AEDs in most patients. We did not find any statistical predictors for long-term patient responses to VNS.

Based on our results, we can summarize that VNS is a safe treatment option in patients with drug-resistant epilepsy with long-term efficacy. In our study, we proved an excellent response to VNS, even in patients treated for 17 years.

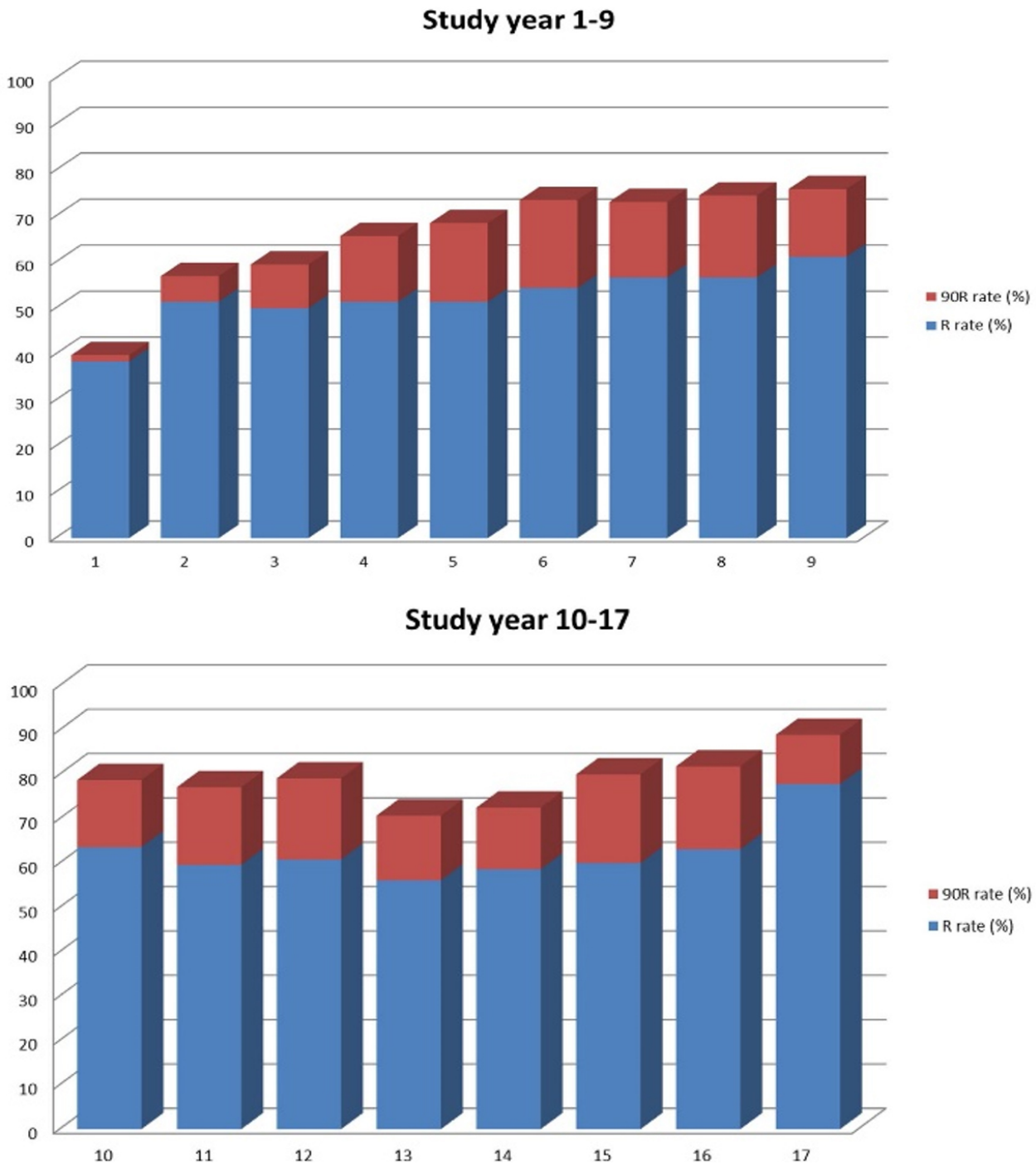

Figure 13: Temporal changes in representation of responders (R) and 90% responders (90% R) in year 1-9 and year 10-17

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Based on improved surgical care, the low risk of complications, and accessibility, VNS is also indicated for older patients with chronic internal disease, and patients with severe intellectual disability are referred for palliative surgery such as VNS (Andriola and Vitale, 2001; Danielsson et al., 2008).

The main aim of our further work was to assess whether even these older patients and patients with severe intellectual disability can profit from VNS implantation (Chrastina et al., 2018a) (Annex 12).

We retrospectively collected data about patients implanted with VNS. The patients were categorized as responders (≥ 50% seizure reduction), 90% responders (≥ 90% seizure reduction), and non-responders (< 50% seizure reduction). The patients were evaluated 1 year after surgery and at their most recent visit after at least 2 years of follow-up care. The patients were divided into groups depending on age (< 40 years versus ≥40 years; < 50 years versus ≥ 50 years; respectively), epilepsy duration (< 20 years versus ≥ 20 years; < 30 years versus ≥ 30 years; < 40 years versus ≥ 40 years; respectively), and presence of intellectual disability (present versus absent).

We identified 103 patients with VNS who had at least one follow-up visit, and 94 patients treated with VNS longer than 2 years. When analyzing the response to VNS therapy, we did not prove significant statistical differences with respect to patient age, epilepsy duration, or presence of intellectual disability, with only two exceptions. First, the patients with epilepsy duration ≥ 20 years tended to be classified more often as responders than patients with epilepsy duration < 20 years at the last follow-up visit (p=0.046). Second, the patients with epilepsy duration ≥ 30 years were more often 90% responders than patients with epilepsy duration < 30 years at the follow-up

visit 1 year after implantation (p=026). Nevertheless, this difference was lost at the last follow-up visit.

It is possible to claim than VNS can be used as a method of therapeutical choice even in patients with higher age, longer epilepsy duration, and severe intellectual disability because all these groups can profit from this treatment.

Limitations of VNS therapy

There are limitations associated with VNS therapy, namely (1) adverse events of VNS therapy, and (2) inability to predict efficacy at the individual patient level.

Adverse events of VNS therapy

In general, adverse events conditioned by VNS are moderate and can be divided into two groups: (a) adverse events related to surgery, and (b) adverse events associated with long-term use.

Adverse events related to surgery include common infections, vocal-cord palsy, lower facial weakness, and bradycardia or systole in the operating room in 0.1% cases. The reason for this rare heart rhythm abnormality is not fully understood; it can be conditioned by abnormal electrode placement, indirect stimulation of the cervical cardiac nerves, technical malfunction, or an idiosyncratic reaction (Ben-Menachem, 2002; Handforth et al., 1998).

The adverse events associated with long-term use include coughing, throat pain, and hoarseness; they tend to improve over time (Handforth et al., 1998; Morris et al., 1999). VNS does not influence blood counts or blood chemistry, including liver function, which is essential information for many patients (Ben-Menachem, 2002).

VNS was implanted in more than 100,000 people around the world in all age groups (Ben-Menachem, 2002; Englot et al., 2017). These 100,000 patients include women of child-bearing age, and there are anecdotal reports about pregnancies, deliveries, and further child development in these patients.

VNS may influence gravidity in both its afferent and efferent fibers. Afferent fibers (forming 80% of the vagus nerve) have connections with cortical and subcortical structures. These fibers, among other things, influence the functioning of the central autonomic system and excretion of neuroendocrine hormones with particular importance of oxytocin for gravidity and child-bearing. Efferent fibers (forming 20% of the vagus nerve) influence mainly the heart functioning, but a small portion projects to the uterus. These fibers may have an impact on uterus functioning during pregnancy and delivery (Sabers et al., 2018; Sato et al., 1996). However, it is necessary to highlight that gravidity, child-development, and delivery are not influenced only by VNS. AEDs, usually in polytherapy, seizures, and concomitant medication play essential roles, and it is impossible to separate their influence. In the future, we plan to focus on this topic.

Prediction of VNS efficacy

The most significant problem associated with VNS therapy is the inability to predict VNS efficacy at the individual patient level. At the moment, it is possible to recognize which patient groups can profit more from VNS treatment. Englot et al., in a meta-analysis of more than 3,321 patients, found that patients with generalized epilepsy and children, especially children younger than six years, exhibit the highest seizure reduction. Regarding etiology, patients with posttraumatic epilepsy and tuberous sclerosis profit the most from VNS (Englot et al., 2011).

However, it is not possible to reliably predict VNS efficacy at the individual level, i.e., based on pre-implantation data. The pre-implantation identification of patients profiting from VNS is crucial for several reasons. Importantly, it can decrease the need for ineffective surgery, improving the allocation of financial costs. Moreover, it can increase the confidence of physicians and patients in neurostimulation.

At the moment, four studies have dealt with pre-implantation VNS efficacy prediction (Babajani-Feremi et al., 2018; Ibrahim et al., 2017; Mithani et al., 2019).

Ibrahim et al. (2017) published a prediction model based on the analysis of resting-state fMRI in a group of 21 children with drug-resistant epilepsy. They demonstrated that thalamocortical connectivity to the anterior cingulate and insular cortices is stronger in responders than in non-responders. They reached an accuracy of 86% in their study. When validating their model on an external dataset of 8 children, the accuracy was almost 90% (Ibrahim et al., 2017).

The study by Babajani-Feremi et al. (2018) predicts VNS efficacy by analyzing resting-state magnetoencephalography (MEG). Resting-state MEG can be used to study and quantify the impact

of epilepsy on the brain networks and the changes of brain networks conditioned by different therapeutical interventions. In this study, the authors made calculations on recorded resting-state MEG using three global graph measures: modularity, transitivity, and characteristic path length, in which they found statistically significant differences between responders and non-responders. Subsequently, they formulated a classifier that was able to predict VNS response with an accuracy of 87% (Babajani-Feremi et al., 2018).

The study by Mithani et al. (2019) proved the differences in white matter microstructures in DTI between responders and non-responders; these differences were subsequently used for the construction of a classifier for VNS response prediction (Mithani et al., 2019).

In our study, we tried to develop a statistical classifier for prediction of VNS response based on the EEG reactivity to external stimuli (Brázdil et al., 2019) (Annex 13).

Our work is based on the finding that synchronization and desynchronization of EEG are responsible for VNS efficacy (Jaseja, 2010; Marrosu et al., 2005). We presumed that inter-individual variability in the EEG ability to synchronize/desynchronize in response to external stimuli conditions a type of response to VNS (responders vs. non-responders). As the next step, we tried to formulate a statistical classifier for predicting response to VNS in an individual patient based on pre-implantation EEG.

We collected data in a group of patients treated with VNS for drug-resistant epilepsy. Patients were categorized as responders or non–responders based on the criteria by McHugh et al. (2007).

In each patient, a standard pre-implantation EEG with photic stimulation and hyperventilation was identified. The EEG was segmented to several time-intervals and filtered to the individual

frequency bands (theta, alpha, beta, gamma). A Hilbert transform was employed to estimate the envelopes of pre-defined pass-band frequency oscillations as a function of time. Subsequently, absolute and relative mean powers were calculated in time intervals for each frequency band. The responders and non-responders were compared using these relative mean powers. Based on the data obtained in the previous steps, we developed a statistical classifier for prediction of VNS efficacy. This model was validated on an independent patient dataset.

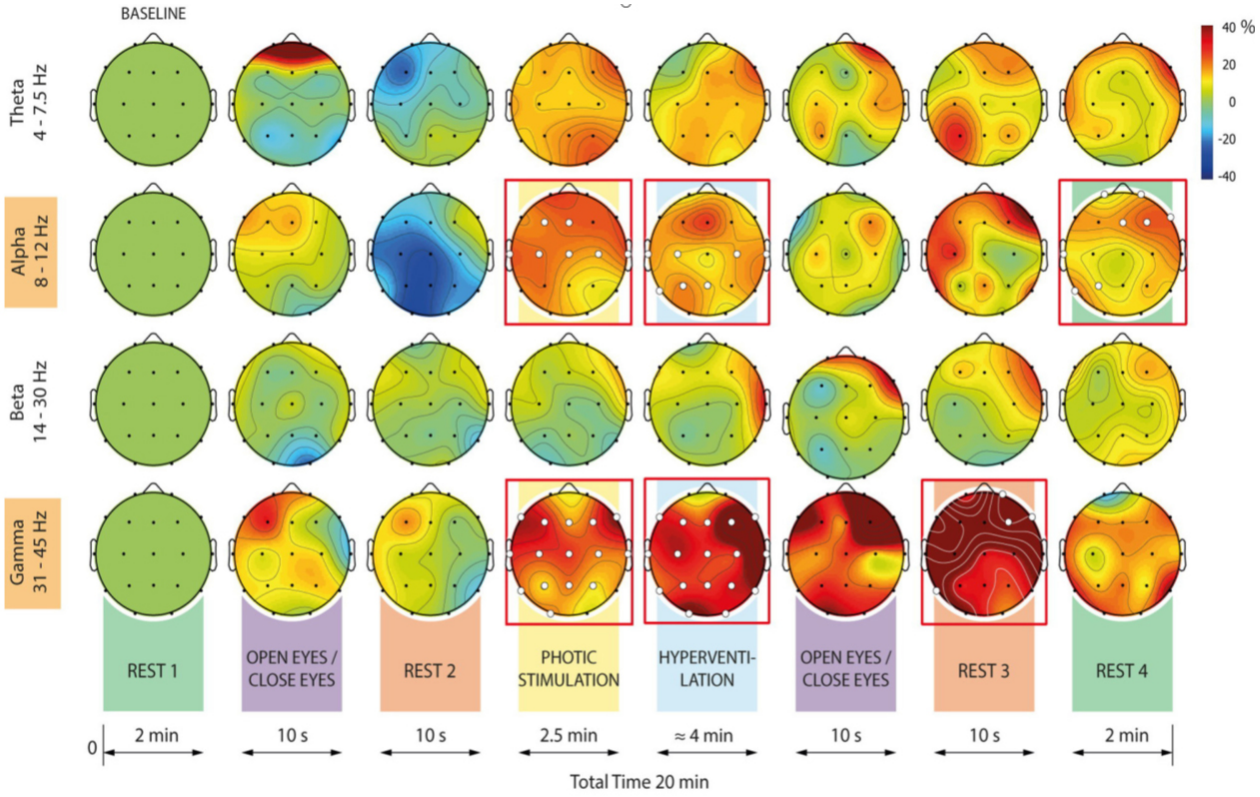

Figure 14: Differences in relative mean powers between responders and non-responders
The differences between responders and non-responders were present mainly in the alpha and gamma frequency during photic stimulation and hyperventilation (white dots). Black dots represent individual electrodes.
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The study included a total of 60 patients treated with VNS: 35 (58%) responders and 25 (42%) non-responders. When relative mean powers were calculated, the differences between responders and non-responders were revealed. These differences were present mainly in the alpha and gamma frequency ranges during photic stimulation and hyperventilation (Figure 14).

In the next step, the statistic classifiers based on the relative mean power changes in (1) areas defined by a group of electrodes or (2) a single electrode were created using automatic machine learning. By this approach, we managed to achieve 86.7% accuracy (88.6% sensitivity and 84% specificity). We then validated this statistical model on the independent patient data (25 patients),

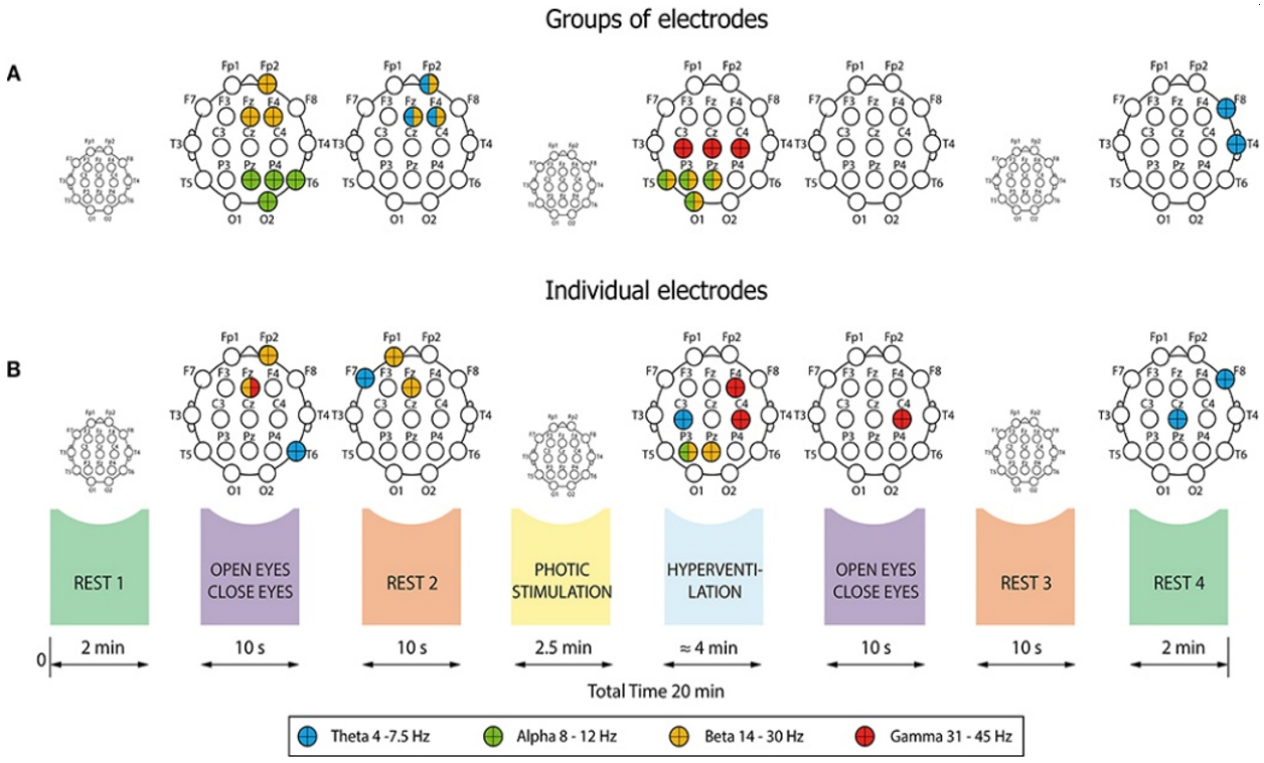

Figure 15: The individual areas (a) and electrodes (b) used for statistic classifiers in each time interval for individual frequency bands
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where we confirmed our results with 86.4% accuracy (83.3% sensitivity, 90% specificity). The groups of electrodes and the individual electrodes chosen for the development of a statistical classifier are shown in Figure 15.

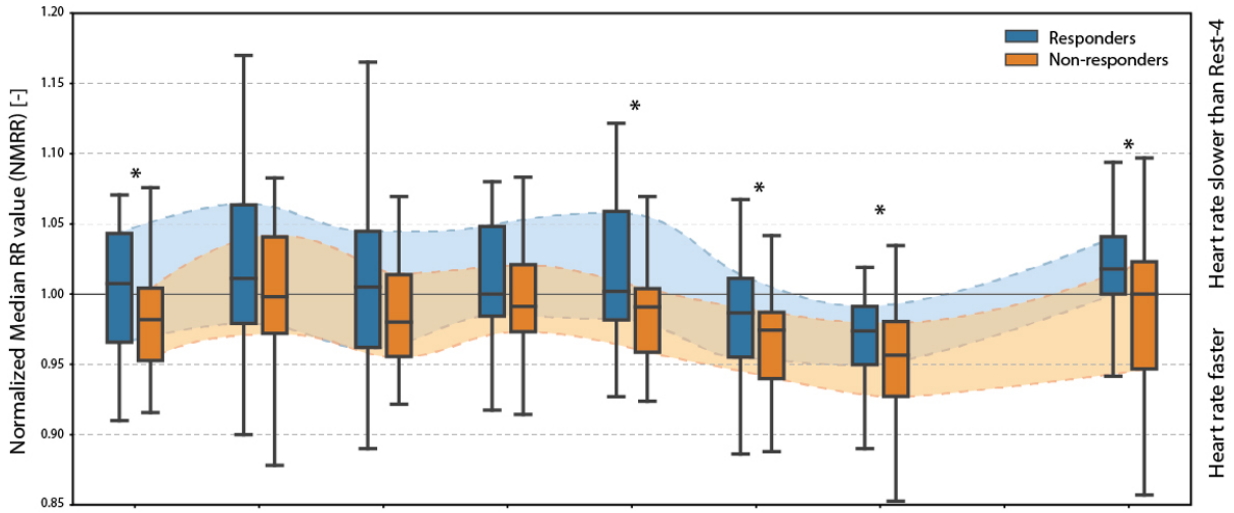
We found differences in the cerebral reactivity to external stimuli between responders and non-responders. These differences were present mainly in photic stimulation and hyperventilation. In the next step, a statistical classifier for predicting VNS efficacy was developed. The accuracy of the classifier was confirmed in an independent patient dataset. We plan to validate our results in another project (see the Future directions section).

Our previous work concerned VNS response prediction based on EEG analysis. However, there are also reports about links between VNS efficacy and heart-rate variability (HRV) based on ECG analysis. Liu et al. (2017) demonstrated that non-responders to VNS have more pronounced impairment of cardiac autonomic functions (Liu et al., 2017).

We tried to confirm this theory in our manuscript (Plesinger et al., submitted) (Annex 14).

The patients were recruited from our previous study based on the availability of quality ECG accompanying EEG recording. The study was done in the following steps: (1) an individual EEG was sub-segmented into 9 time intervals: Rest 1, Eyes-opening 1, Rest 2, Photic stimulation, Hyperventilation by mouth, Hyperventilation by nose, Rest 4, Eyes-opening 2; (2) the individual heartbeats were detected, and heartbeat intervals (RR intervals) were estimated; (3) median RR (MRR) were counted in each time interval; (4) MRRs were normalized to baseline at Rest 4, which led to the estimation of normalized MRR (NMRR); and (5) statistical differences in MRR and in NMRR between responders and non-responders were counted; the Area Under The Receiver-Operator Curve (AUC) was determined.

We included a total of 66 patients from the source study. We did not find any statistical differences between the responders and non-responders in MRR. However, when normalization was performed, the differences in NMRR were present in 5 time intervals: Rest 1, Rest 3, Hyperventilation by nose, Hyperventilation by mouth, and Eyes-opening 2 (Figure 16).



	Rest 1	Eyes Open 1	Rest 2	Photic stimulation	Rest 3	Hyperventilation by Nose	Hyperventilation by Mouth	Rest 4 (baseline)	Eyes Open 2
p-value	0.038	0.141	0.075	0.110	0.013	0.033	0.028		0.023
AUC	0.627	0.578	0.603	0.588	0.659	0.631	0.637		0.644

Figure 16. The separation of responders and non-responders based on normalization of median RR (NMRR) interval

- 1st and 3rd quartile of specific boxplots marked by blue and orange stripes

- significant features marked in gray

ECG can provide additional information in the prediction of VNS efficacy. It will probably be helpful in the construction of a statistical classifier. We plan to employ this method in our future research.

Deep brain stimulation of the anterior nucleus of the thalamus (ANT-DBS) in epilepsy

DBS is a common and effective therapeutic method for patients with movement disorders, particularly Parkinson's disease. Despite the extensive experience with DBS in this field, there is substantially less knowledge about DBS as a treatment for refractory epilepsy. ANT-DBS is currently approved as a therapeutic option for the treatment of drug-resistant epilepsy in Europe, the USA, Canada, and Australia (Li and Cook, 2018).

The ANT was chosen as a suitable target for its anatomical and functional position. The ANT is part of the "Papez circuit" and has dense afferent connections from the hippocampus both directly via the fornix and indirectly via the mammillothalamic tract. There are other afferent fibers to the ANT from the anterior cingulate cortex, posterior cingulate cortex, retrosplenial cortex, and inferior parietal lobule. The efferent fibers project mainly to the hippocampus (Child and Benarroch, 2013). Despite this detailed information about ANT anatomy and function, the precise mechanism of action of ANT-DBS is not fully understood (Child and Benarroch, 2013).

The first ideas of thalamic stimulation as a suitable treatment for neurological diseases, including epilepsy, were introduced in the 1970s and 1980s (Cooper, et al., 1980). The importance of ANT for seizure genesis/suppression was first proven in experimental animal studies (Mirski and Ferrendelli, 1984, 1986; Mirski et al., 1986; Mirski et al., 1997). This led to pilot studies in humans (Andrade et al., 2006; Hodaie et al., 2002; Kerrigan et al., 2004; Lee et al., 2006a; Lim et al., 2007; Osorio et al., 2007).

DBS – efficacy and adverse events

Hodaie et al. (2002) implanted a group of 5 patients with ANT-DBS, which caused significant seizure reduction (the seizure reduction ranged from 33% to 89%; mean seizure reduction was 54%), the implantation and stimulation did not elicit any significant adverse events or any behavioral changes (Hodaie et al., 2002). Other preliminary studies also had satisfying results (Andrade et al., 2006; Kerrigan et al., 2004; Lee et al., 2006a; Lim et al., 2007; Osorio et al., 2007). Based on this, the study of Stimulation of the Anterior Nuclei of Thalamus (SANTE study) was initiated (Fisher et al., 2010).

The SANTE study was a multicenter, double-blind, randomized trial of bilateral ANT stimulation for focal epilepsy. The SANTE study was divided into two phases: the blinded phase (the first three months) and the unblinded phase (subsequent 21 months). In the blinded phase, patients were randomized into a stimulated group and a non-stimulated group. In the next phase, all patients received stimulation. At the end of the blinded phase, the stimulated group reported significantly higher seizure reduction than the control group: a 29% greater reduction in seizure frequency in the stimulated group. During the two years of follow-up care, the authors proved the long-term efficacy of ANT-DBS (there was a 56% median reduction in seizure frequency, 54% patients were responders [≥50% seizure reduction], and 12% patients were seizure-free for at least six months) [30].

The follow-up care of patients within the SANTE study continued, and Salanova et al. (2015) reported about the ANT-DBS efficacy in 5 years (Salanova et al., 2015). Seventy-five (68%) patients out of the 110 initially implanted patients remained in the study. In the 5th year, the median seizure reduction was 69%, the responder rate was 68%, and 16% of patients were seizure-free at

least for six months. A similar trend is present with VNS; the percent representation of patients with favorable responses to stimulation increases over time, though the precise reason for this phenomenon remains still speculative.

The most common adverse events of ANT-DBS during the first year of the SANTE study were as follows: paresthesias (18% patients), pain in the implant site (10.9% patients), and infection in implant site (9.1% patients) (Fisher et al., 2010).

During the five years of follow-up care, device-related adverse events and other adverse events were reported (Salanova et al., 2015). The device-related adverse events were pain in the implant site (23.6% patients), paresthesias in the implant site (22.7% patients), implant site infection (12.7% patients), therapeutic product ineffective (10% patients), discomfort (9.1% patients), lead(s) not within target (8.2% patients), sensory disturbance (8.2% patients), memory impairment (7.3% patients), implant site inflammation (7.3% patients), dizziness (6.4% of patients), postprocedural pain (6.4% patients), extension fracture (5.5% of patients), and neurostimulator migration (5.5% patients). Infection led to the explantation of the system in nine patients (five patients experienced complete system explantation, four had partial explantation).

Depression, memory impairment, suicidal ideation, and deaths ranked among other adverse events. Depression was present in 37.3% of patients (3 events in 3 subjects were considered to be device-related). Memory impairment was present in 27.3% patients (approximately a third of memory impairment was confirmed by neuropsychological examination). Suicidal ideation was reported by 11.8% (1 subject committed suicide; the suicide was not believed to be device-related). Seven patients died during the study – 1 probable sudden unexpected death in epilepsy (SUDEP), 2 definite SUDEP, and 1 possible SUDEP.

The explanation for psychiatric side effects is supported by the role of the ANT in the "Papez circuit," which is crucial for emotional and cognitive control. In general, there are no reliable data regarding psychiatric side effects. Järvenpää et al. (2018) reported remarkable results when analyzing a group of 22 patients with ANT-DBS (Järvenpää et al., 2018). The authors did not find any changes in psychological tests at the whole group level. However, transient mood disorders were present in four patients – two patients reported sudden-onset depressive and melancholic symptoms, and the other two reported slowly-progressive psychiatric symptoms, including irritation, sleep disturbances, anxiety, fear, and paranoid symptoms. All previously mentioned symptoms disappeared after adjusting the stimulation current or changing the stimulation parameters. Novais et al. (2019) reported that ANT-DBS is associated with impaired psychological functions after surgery, as well as a bilateral epileptogenic zone and a lack of remission of disabling seizures (Novais et al., 2019).

In our center, we have experience with the development of de novo psychopathology related to ANT-DBS (Doležalová et al., 2019) (Annex 15).

The patient is a female born in 1970 with a family history of mesial temporal lobe epilepsy. The epilepsy was characterized as focal bitemporal based on scalp EEG. There was a right-sided HS on MRI, but the Wada test showed the crucial role of the right-sided hippocampus for memory. The patient was implanted with VNS, which was inefficient and was explanted. The patient was offered ANT-DBS implantation at the age of 41 years. She was not treated for psychiatric illness, which was confirmed by neuropsychological examination. However, psychology tests revealed echolalia, perseveration, and the global deterioration of cognitive function (IQ 72, the most severe alteration in execution and memory). After implantation, the monopolar stimulation of the most proximal

contacts (contact 3 on the left and contact 11 on the right, Figure 17) was initialized. After implantation, the patient did not report the decrease of seizure frequency, but ANT-DBS influenced seizure severity and duration positively.

The PSEs started to appear 3 months after stimulation initialization. The patient's family started to complain about irritability, hostility, and aggressiveness, which were accompanied by paranoid production. The patient reported that ANT-DBS influenced her behavior and forced her to walk backward. The situation worsened when anyone was speaking about DBS. The psychological and psychiatric examinations confirmed incoherent thoughts, behavioral and emotional alteration, and disordered personality and behavior. The stimulation was discontinued, but the patient has not yet

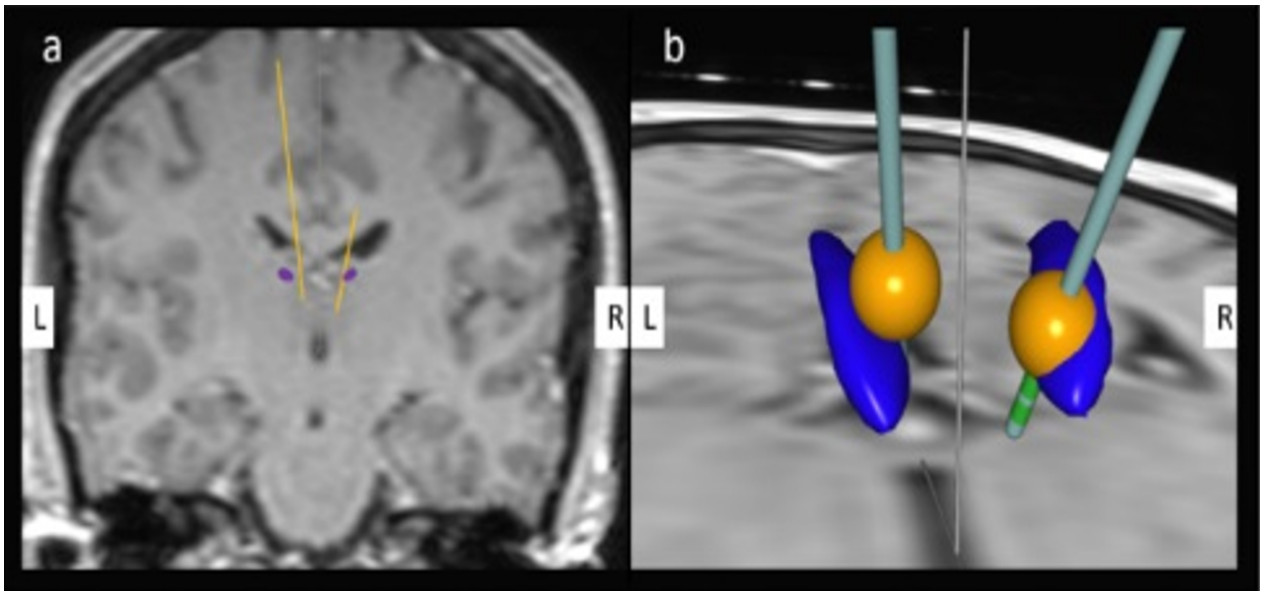


Figure 17: The relation between the ANT and DBS electrodes
Panel a shows the relation between the ANT (violet) and electrodes in a coronal section.
Panel b illustrates the estimated distribution of the electrical field (yellow) during stimulation and its links to the ANT (blue). We chose a correct contact on the right, but a more distal contact would be in a more suitable position on the left.
L – left, R – right; SureTune software (Medtronic, Minneapolis, MN, USA).
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returned to her pre-implantation level, as supported by repeated psychiatric hospitalizations. In this patient, we suspect that the implantation of DBS electrodes caused some alteration in thalamic circuits that had long-term consequences.

DBS – electrophysiological aspects

From the electrophysiological point of view, it is remarkable to record the changes of scalp EEG in association with DBS or the intracerebral activity recorded directly from the ANT via intracerebral electrodes. Kerrigan et al. (2004) reported the presence of changes, so-called driving response, of scalp EEG conditioned by the stimulation of the ANT. This response was time and frequency locked to ANT stimulation (Kerrigan et al., 2004b).

We recorded the cerebral signal from electrodes implanted in the ANT (Rektor et al., 2016) (Annex 16).

We reported the interictal and ictal recordings from the ANT in six patients. The recordings from ANT-DBS was obtained in a similar way as recordings from DBS in patients with Parkinson's disease, i.e., DBS was implanted and the electrodes were left externalized for recording. After several days, the internalization was performed.

Interictal recording

No IEDs were found in the ANT. However, HFOs up to 240 Hz. were recorded in all patients. We even recorded HFOs up to 500 Hz in one patient. The interictal HFOs are shown in Figure 18.

Ictal recording

We recorded ictally an early broadband increase of power in all seizures (Figure 19). Moreover, a specific ictal activity was present in one seizure; this ictal activity preceded the clinical onset in a given seizure (Figure 20).

To our knowledge, this is the first described occurrence of HFOs in subcortical structures.

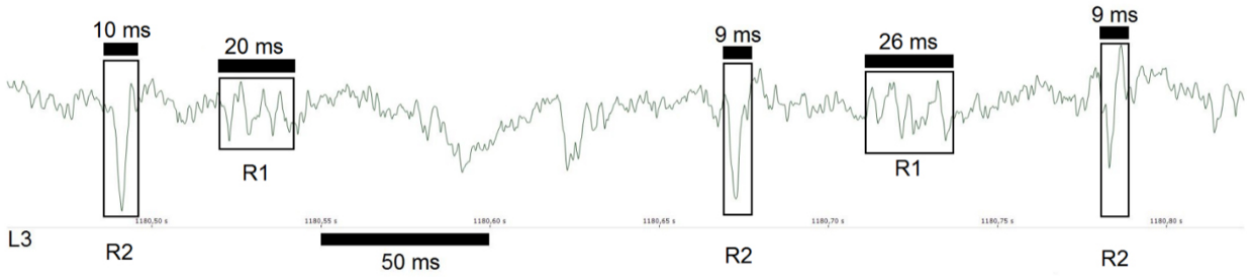

Figure 18: The High-frequency oscillations (HFOs) recorded in nucleus anterior thalami (ANT)

The figure demonstrates HFOs recorded in ANT, raw signal, sampling frequency 5kHz. Two types of HFOs are shown: (1) periodical HFOs – longer rectangle (lasting >20 ms, R1); (2) single peaks (burst) – shorten rectangle (lasting <10 ms, R2).

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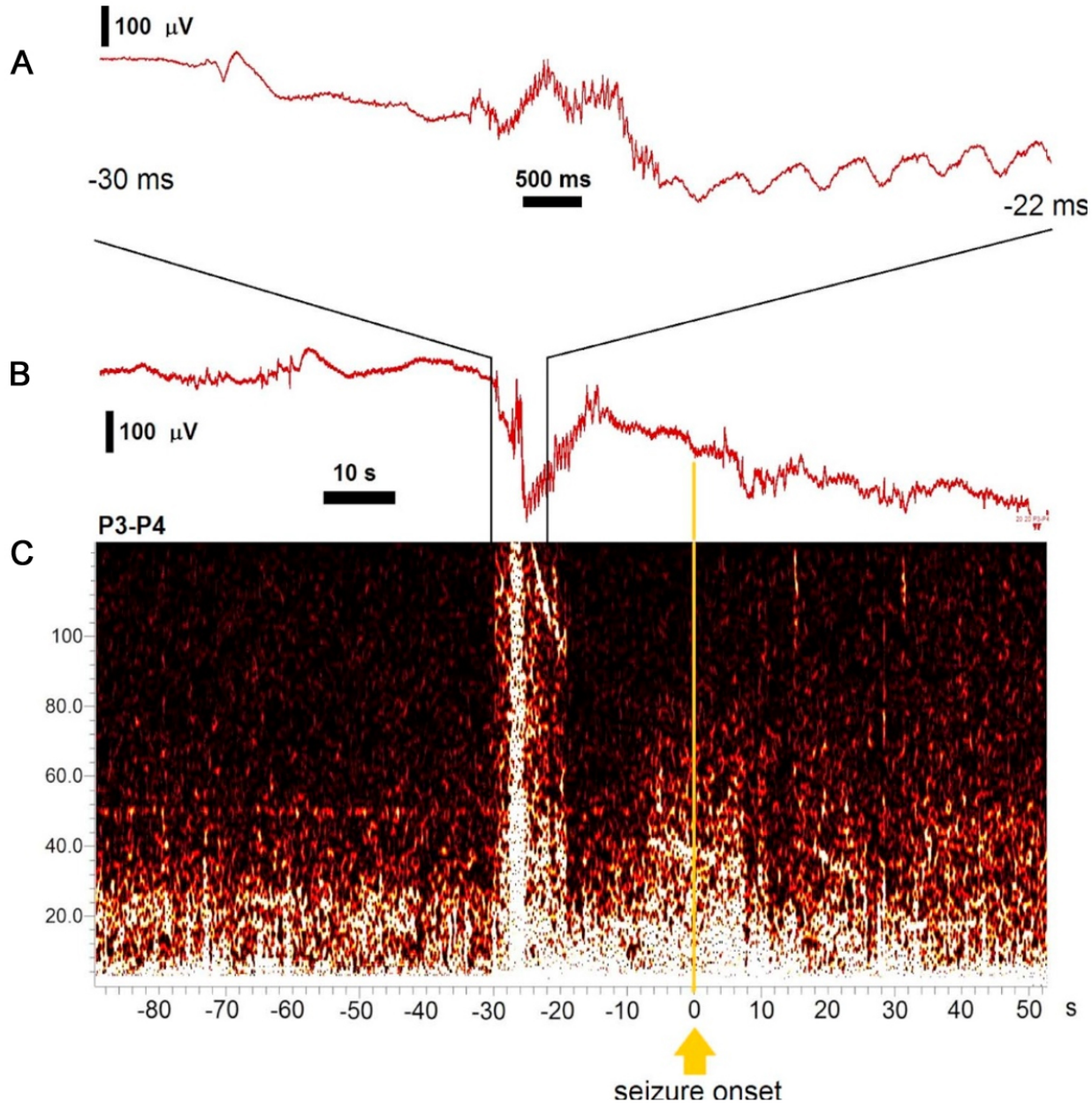

Figure 19: Preictal recording in the ANT – preictal broadband increase in all power spectra

A: Enlargement of raw signal from 30 ms to 22 ms before seizure onset

B: Raw signal – time window 90 ms before and 50 ms after seizure onset

C: Normalized Time Frequency Maps with preictal broadband increase in all power spectra. Yellow vertical line – clinical seizure onset

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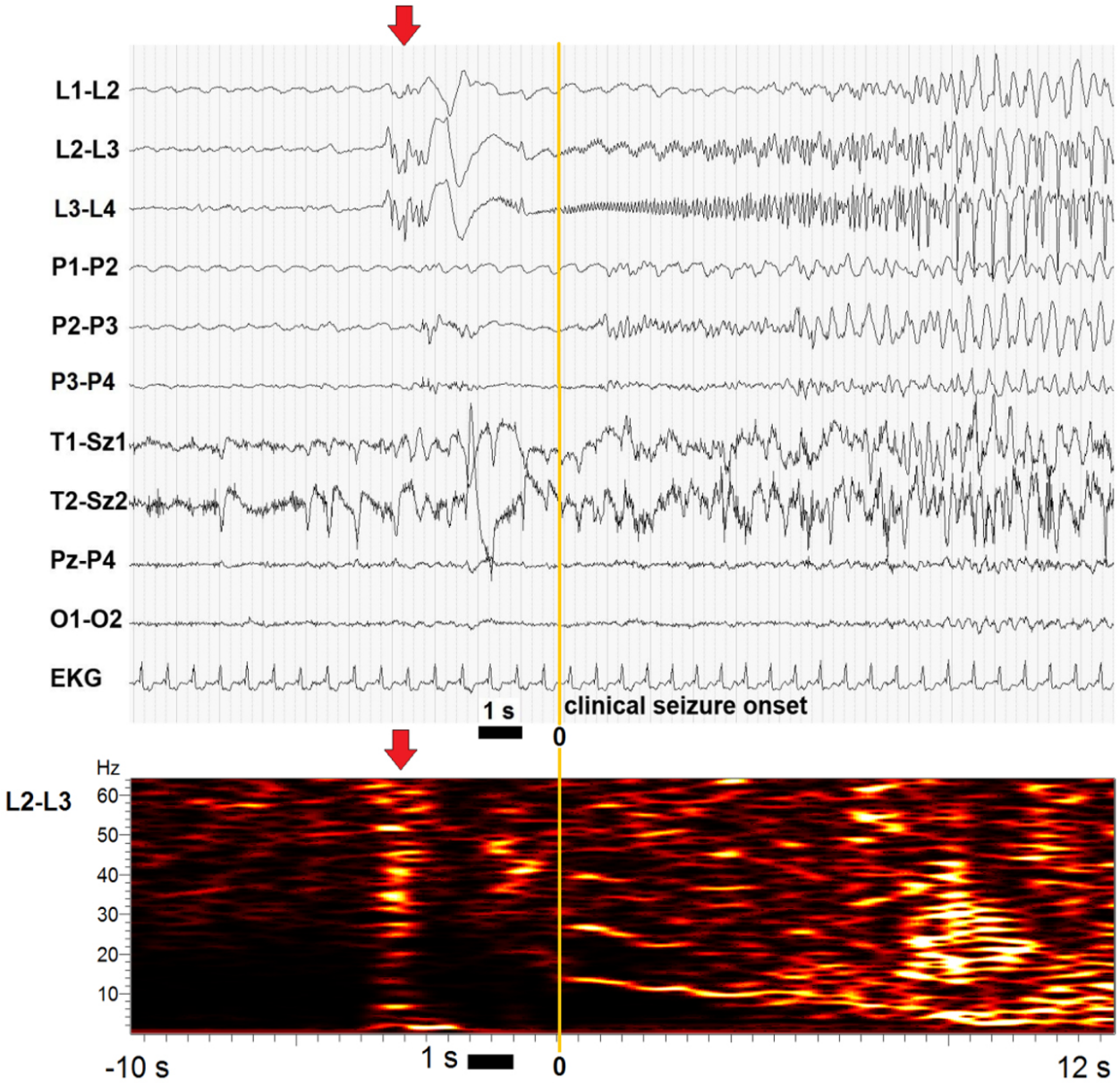

Figure 20: The clinical seizure onset (vertical yellow line) was preceded by clear-cut rhythmic activity in the left ANT, contacts L2-L3

Upper panel: The rhythmic activity could be seen first in the left ANT (red arrow); it then spreads to the right ANT.

Bottom panel: Normalized Time Frequency Maps.

Assumed from Rektor et al., 2016; published with permission.

Responsive neurostimulation (RNS)

RNS was approved for clinical use in the US in 2013. This method differs widely from VNS and DBS, which are based on an open-loop approach, i.e., they derive pulses on a fixed schedule. RNS derives stimulation only in the presence of ictal discharges, i.e., it works as a closed loop.

RNS is surgically implanted in the cranium and is connected to the skull. The device contains leads (subdural strips or depth electrodes) for monitoring brain activity. These leads are implanted through the burr holes or craniotomy to the proximity of the presumed seizure onset zone.

The unequivocal condition for implantation of RNS is a hypothesis about seizure onset zone localization. For successful resective surgery, it is necessary to have a precise delineation of the epileptogenic zone. The hypothesis for RNS can be weaker; it is sufficient to implant RNS somewhere in the epileptogenic network to obtain a sufficient clinical response (Geller, 2018).

Benefits of surgery

Impact on seizure frequency

With classical resective surgery, the best modality for measuring success is seizure freedom. The seizure freedom rates are the highest in TLE; approximately 70% of patients are seizure-free after surgery. There are differences between lesional and nonlesional TLE: in patients with lesional TLE, 75% of cases are seizure-free; the representation of seizure-free patients decreases to 51% in nonlesional cases.

The numbers of seizure-free patients in ETLE are lower than in TLE; in this group, 46% of patients report complete seizure freedom after surgery. In these ETLE, the difference between lesional and nonlesional cases is high. The number of seizure-free patients is almost comparable to TLE in lesional cases (seizure freedom in 60% of lesional ETLE). However, the reported numbers in nonlesional ETLE are much lower; only one-third of patients experienced complete seizure cessation in this subgroup (Téllez-Zenteno et al., 2010).

The use of any neurostimulation methods only rarely leads to seizure freedom. The efficacy of these methods can be measured by responder rates (patients experiencing≥ 50% seizure reduction). The responder rates are comparable among all neurostimulation methods; approximately 50% of patients are classified as responders after the first year of stimulation (a more detailed description is provided in the relevant chapters) (Ben-Menachem et al., 1994; Fisher et al., 2010; Handforth et al., 1998; Salanova et al., 2015).

Impact on the quality of life, employment status, and other variables

Importantly, successful neurosurgery constitutes an effective therapy for epileptic seizures and may also reduce comorbidities (e.g., depression and cognitive deficits), improve quality of life (QOL), and increase social reinsertion, including employment; moreover, it reduces long-term morbidity and mortality (Picot et al., 2016).

For the impact of epilepsy surgery on QOL, Seiam et al. (2011) identified 32 studies published between 1950 and 2008 focusing on this topic. Twenty-nine (90.6%) out of these 32 reports described a significant positive effect. The remaining three studies did not prove an association of surgery with the improvement of QOL. Seiam et al. (2011) identified some methodological insufficiencies in those studies, such as an inappropriate choice of a questionnaire or a small sample size. The determinants predicting the improvement of QOL were both preoperative and postoperative. Preoperative anxiety and depression or poor baseline psychological functions are associated with lower postoperative QOL. The increase of QOL can also be attributed to seizure control, a robust surgical placebo effect, or the reduction of adverse events related to AEDs in cases with daily dose reduction. The complete cessation of "disabling" seizures is crucial for the improvement of QOL. The patients with "only" seizure reduction reported five times less improvement of QOL than seizure-free patients. On the other hand, the persistence of auras did not condition worse QOL (Seiam et al., 2011).

In our study, we tried to determine the impact of surgery on daily life, including QOL (Doležalová et al., 2016b) (Annex 17)**.**

We designed a questionnaire with 13 items. The items were divided into four main topics: (1) demographic data, (2) information regarding surgery, (3) social issues (employment status and driving license), (4) subjective evaluation of surgery benefits. The questionnaires were sent to 137 patients who underwent surgery in our center with at least one year of follow-up care.

We included 91 respondents who correctly completed the questionnaire (56 men, 35 women). Of those, 59 (64.8%) were seizure-free after surgery. After surgery, there was a slight increase in the number of employed patients (46 [50.5%] patients were employed before surgery in comparison to 50 [54.9%] patients after surgery). This increase was dependent on gender, i.e., present only in the male subgroup. Nineteen (20.9%) patients obtained driving permission after surgery ($p<0.001$). Forty-nine (53.8%) patients reported an increase of QOL after surgery. The only variable that was related to the increment of QOL after surgery was employment status (the patients who were employed after surgery reported a higher QOL, $p=0.037$).

To conclude our results, the surgery can bring a chance for seizure cessation and improvement of QOL, but in general, it has a low impact on employment status. This fact offers an opportunity for social interventions or occupational therapy with the goal of employment status improvement.

Future directions

In our future research, we would like to extend our attention in two directions. The first direction is related to the development of the prediction paradigm for neurostimulation (VNS, DBS). The second direction concerns seizure detectors and proof of their clinical utility.

The development of the prediction paradigm for neurostimulation

Neurostimulation methods offer a high probability of substantial seizure reduction (Fisher et al., 2010; Harroud et al., 2012; Ma and Rao, 2018; McIntosh et al., 2004; Orosz et al., 2014; Ryvlin et al., 2014; Ryvlin and Kahane, 2005; Salanova et al., 2005). Despite large groups of implanted patients and many attempts, it is not possible to predict the effectiveness or benefits for an individual patient (Englot et al., 2011; Englot et al., 2016). This fact brings uncertainty into the patient decision-making and may decrease the credibility of neurostimulation as a treatment for drug-resistant epilepsy.

We have developed a statistical classifier that can predict the benefit of VNS treatment with high accuracy (sensitivity and specificity) (Brázdil et al., 2019). Despite this success, we have to challenge the limitations of our previous work. The gaps in our previous work could be summarized as follows: (1) the age-limited validity; (2) the absence of confirmation in independent datasets; and (3) the absence of prospective study. We want to close these gaps using a grant already started in 2019 (Ministry of Health of the Czech Republic, grant 19-04-00343).

First, we based the statistical model on data recorded only in adult patients. It means that this model could be applied only for predictions in adults, which contrasts with current praxis when one-third of all implanted patients are children. Moreover, children seem to be better candidates for VNS

therapy because they have higher responder rates than adults (Englot et al., 2011; Soleman et al., 2018). Based on these findings, we want to try to develop a similar prediction algorithm that could be applied even to children. We expect that this work will be more challenging because of the higher variability of children's EEG conditioned by brain maturation (Benninger et al., 1984).

Second, the absence of current model validation on an external independent patient dataset is presumably the most significant limitation of our study. We want to overcome this limitation through international collaboration with a foreign epilepsy center, where we plan to retrospectively recruit patients already treated with VNS.

Third, we plan to design and conduct a prospective multicenter study for the prediction of VNS efficacy. We want to initiate a study called PRECISE (Prediction of vagus nerve stimulation EfficaCy In drug-reSistant Epilepsy, Figure 21). The principal aim of PRECISE is to verify the predictability of VNS efficacy by analyzing the pre-implantation routine EEG. Patients will be classified according to their predicted outcome (predicted responders versus predicted non-responders). After the first and the second year of the study, the real-life outcomes (real-life responder versus real-life non-responder) will be determined. The predicted outcomes and real-life outcomes will be compared in terms of accuracy, specificity, and sensitivity. In the meantime, the patients will be managed according to the best clinical practice to obtain the best therapeutical response.

Fourth, we would like to verify whether it is possible to extrapolate our experience with VNS to ANT-DBS. It seems feasible based on neuroanatomical, experimental, and clinical knowledge. A vagus nerve consists of 80% afferent fibers that transmit information from visceral organs to the nucleus tractus solitarius. There are dense connections between the nucleus tractus solitarius and

other higher centers, namely, the hypothalamus, dorsal raphe, nucleus ambigus, dorsal motor nucleus of the vagus nerve, amygdala, and thalamus (Rutecki, 1990). The influence of VNS on

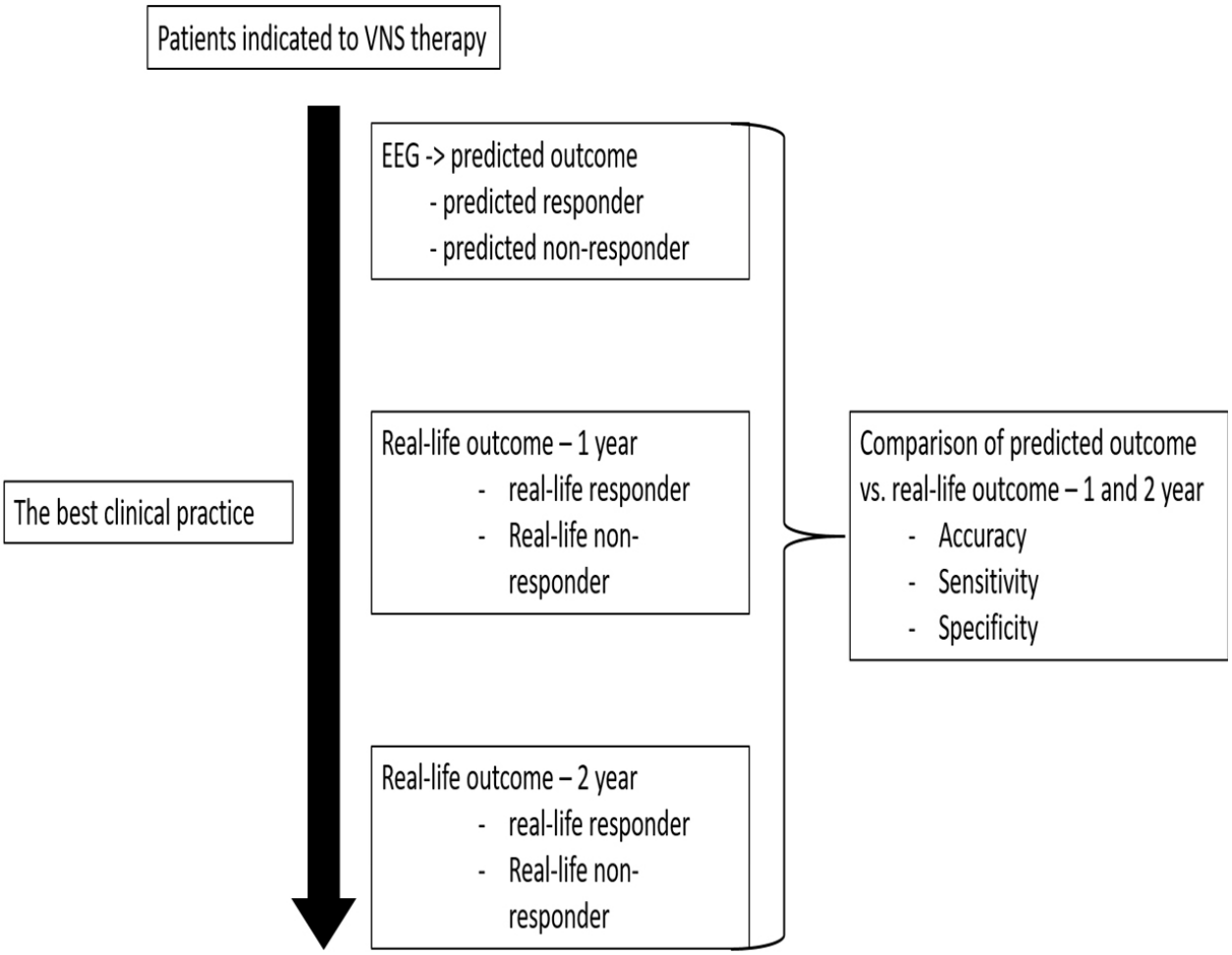

Figure 21: Design of prospective study PRECISE (Prediction of vagal nerve stimulation EfficaCy In drug-reSistant Epilepsy
The figure represent patient flow within planned prospective study PRECISE

higher brain structures was demonstrated by both PET and fMRI (Ko et al., 1996; Rutecki, 1990). PET studies showed increased perfusion in the inferior cerebellum, hypothalamus, and thalamus; the decreased perfusion was present in the hippocampus, amygdala, and posterior cingulate gyrus.

In subsequent studies, the authors proved the increased bilateral thalamic cerebral blood flow, which correlated with decreased seizure frequency. To conclude, it seems that thalamus and limbic structures are actively involved in VNS therapy, i.e., we can expect the involvement of similar circuits as during ANT-DBS (Ben-Menachem et al., 1994). These theories could be supported by a recently published clinical study that proved a similar pattern of response in VNS and DBS treatment (Kulju et al., 2018). Based on these statements, we can expect that a similar algorithm for efficacy prediction can be postulated even for ANT-DBS. The work with ANT-DBS will be influenced by relatively low numbers of implanted patients in each center, so international collaboration will be needed.

Seizure detectors

The next area of our future interest is real-life seizure detection. We want to center our attention on commercial detection systems and test them in ordinary patient environments, i.e., outside of the video EEG monitoring units. Our goal is to examine their utility and their benefits for patients and their families.

The seizure detection systems could be divided into EEG-based detectors and non-EEG-based detectors (van Andel et al., 2016).

EEG-based detectors

EEG-based detectors are not routinely used, and at the moment there is no commercial EEG-based detector. This fact is conditioned mainly by technical limitations (van Andel et al., 2016). In the case of "classic" scalp EEG, the limitations are associated with the presence of electrodes on the patients' heads; the electrodes are thought to be non-aesthetic and bothersome during long-term

use. This restraint could be at least partially overcome by the reduction of electrode size, e.g., by ear electrodes (Looney et al., 2012), which seem to be suitable for recording epileptic activity (Mikkelsen et al., 2015; Zibrandtsen et al., 2017). Earlier studies had to combat the disruption of EEG signals with artifacts, mainly from movements (Pauri et al., 1992); more recently developed algorithms for artifact rejection has improved the accuracy of these detections (Duun-Henriksen et al., 2012; Hopfengartner et al., 2014; Ramgopal et al., 2014). This progress increases the chance of developing commercial EEG-based detectors in the future.

Non-EEG-based detectors

Non-EEG-based detectors are currently used in daily praxis. These detectors analyze the physiological parameters that change at the beginning of seizures. They work as sensors analyzing movements (accelerometers, gyroscopes, magnetometers, electromyography [EMG], mattress-based sensors, or cameras), electrocardiography (ECG; changes of heart rate or heart-rate variability), and electrodermal activity. It seems that mainly the combination of individual sensors enables them to reach high accuracy (Osorio and Schachter, 2011).

Figure 22: Bracelet-like detector Embrace 2 produced by Empatica

The detectors, except mattress-based sensors and cameras, are bracelet-like or watch-like, so they are suitable for daily wear and are not intrusive (Figure 22). The mechanism of the detector function is illustrated in Figure 23. The detector analyzes physiological parameters. If there is a relevant change indicating a seizure onset, the detector sends a signal to the patient's mobile phone via wireless technology. The mobile phone then transmits a message to the patient's family members or caregivers. The patient can personally stop the warning message at several levels to reduce the number of incorrect reports.

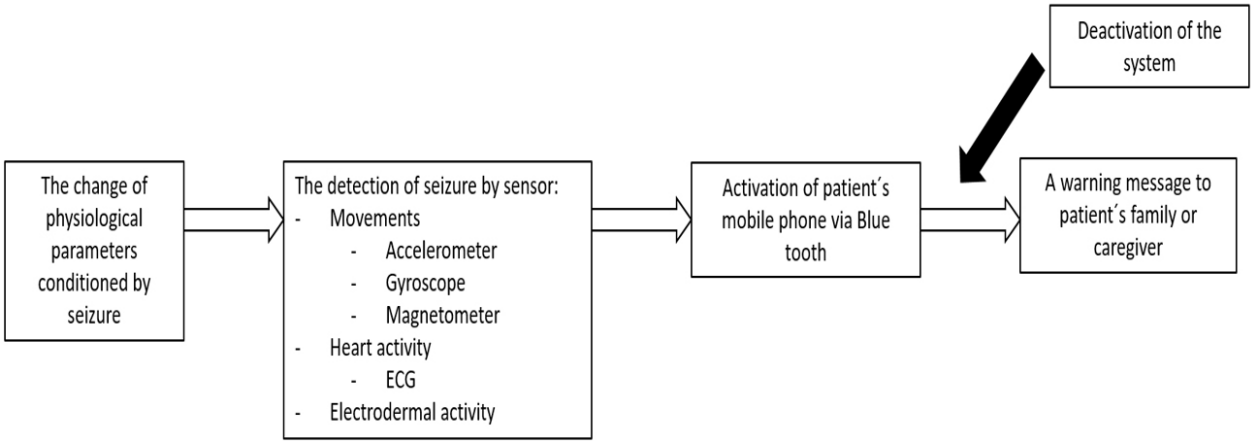

Figure 23: The mechanism of EEG-based detector functions
The figure illustrates the mechanism of functions of non-EEG detectors in several steps.

The information about detector accuracy is valuable for both physicians and patients. The accuracy of detectors is described in terms of sensitivity (the percent representation of correctly detected seizures) and by false alarm/false detection rates (the number of false detections during a defined time interval, usually 8 or 24 hours). High detection accuracy is required; patients and their families do not want to be disturbed by false messages.

In the most recent review of literature focusing on the accuracy of seizure detection, the authors identified five studies reporting data about the accuracy of seizure detectors (Leijten and Dutch TeleEpilepsy Consortium, 2018). Almost all the studies took place in the environment of a video EEG monitoring unit. At the moment, there is very little data about seizure detector efficacy in a "normal" real-life environment. The best results were published by Onorati et al. (2017), who reported a 95% sensitivity and a false alarm rate of 0.07 per 8 hours (Onorati et al., 2017), which seems to be promising.

Benefits of seizure detectors

We believe that seizure detectors can benefit patients and everyone involved in their care, including caregivers, physicians, researchers, and pharmaceutical companies.

Seizure detectors can decrease the risk of sudden unexpected death in epilepsy (SUDEP) or status epilepticus, which are rare but dreaded complications of epilepsy. The lifelong risk of SUDEP in a

patient treated with drug-resistant epilepsy is around 10% (Thurman et al., 2014). SUDEP is most often sleep-related and unwitnessed. Nocturnal supervision is recommended in high risk patients (Ryvlin et al., 2013; Shorvon and Tomson, 2011). However, whole-night supervision means the loss of privacy for both patients and their families. Moreover, it can be exhausting. It is possible that seizure detectors represent an acceptable form of nocturnal supervision for patients at risk for SUDEP (van Andel et al., 2016). The risk of status epilepticus correlates negatively with intervention time-lag between seizure onset and interventions, i.e., patients who are quickly given rescue medication are at a lower risk of status epilepticus than patients whose treatment is delayed or not treated (Neligan and Shorvon, 2011). Seizure detectors can shorten this time lag, which could have a positive impact on the status of epilepticus incidence. We cannot expect the decline of

injuries associated with seizure, because injuries are usually time-related to seizure onset. They happen immediately after a seizure starts and probably cannot be prevented (Nguyen and Téllez-Zenteno, 2009).

Seizures, status epilepticus, and SUDEP mean stress for the patients and their families and caregivers. This stress increases anxiety and has a negative influence on the quality of life. The detectors could potentially decrease the fear of ongoing seizures, and subsequently improve the quality of life (van Andel et al., 2009).

Moreover, the quality of patient lives can be negatively influenced by the attitude of some professional care providers. Epilepsy is, in some individuals, associated with mental retardation, which implies the necessity of whole day professional care and institutionalization. Some social institutes refuse people with active epilepsy because of their fear of seizures, associated injuries, SUDEP, and legal consequences. At the moment, there are no standards for surveillance in patients in social and nursing institutions. We anticipate that the detectors will represent a tool or an alternative for surveillance in these institutionalized patients (van Andel et al., 2016).

Finally, the detectors can provide precise information about seizure frequency, severity, and duration. This information could be helpful for physicians in tailoring medication or for pharmaceutical companies developing medication. It is currently necessary to rely on the information in patient seizure diaries, which can be misinterpreted (van Andel et al., 2016).

We plan to initiate a prospective study in which patients will be equipped with seizure detectors for a defined period. At the beginning and the end of the study, patients will be given a

questionnaire regarding seizure frequency, quality of life, and depression. The patient responses will be compared, and the impact of detectors on patient lives will be evaluated.

Conclusion

Epileptology is an exciting branch of clinical neurology. It has been undergoing a revolution since the late 20th century. This revolution is conditioned by the shift from therapy with sodium bromide to the use of modern AEDs, MRI scanners, IEEG, MRI post-processing methods, and other techniques. I believe that we can still anticipate a significant paradigmatic shift towards the broader use of genetic therapy, individualized virtual brains for tailoring surgical procedures, optogenetics, and other methods that are currently limited to research laboratories. It may sound like science fiction today, but the future holds possibilities that will make our work even more remarkable and will improve the level of care for our patients.

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Annex 1: Dolezalova I, Brazdil M, Hermanova M, Janousova E, Kuba R. Effect of partial drug withdrawal on the lateralization of interictal epileptiform discharges and its relationship to surgical outcome in patients with hippocampal sclerosis. Epilepsy Research 2014;108(8):1406-1416.

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Epilepsy Research (2014) **108**, 1406—1416

journal homepage: www.elsevier.com/locate/epilepsyres

Effect of partial drug withdrawal on the lateralization of interictal epileptiform discharges and its relationship to surgical outcome in patients with hippocampal sclerosis

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Received 9 November 2013; received in revised form 20 May 2014; accepted 13 June 2014
Available online 5 July 2014

KEYWORDS
Epilepsy;
Hippocampal sclerosis;
Outcome;
Interictal epileptiform discharges (IEDs);
Unitemporal IEDs;
Bitemporal IEDs

Summary
Objective: To assess changes in the relative lateralization of interictal epileptiform discharges (IEDs) and interictal EEG prognostic value in terms of surgical outcome between periods with full medication (FMP) and reduced medication (RMP) in patients with temporal lobe epilepsy (TLE) associated with hippocampal sclerosis (HS).
Methods: Interictal scalp EEGs of 43 patients were evaluated for the presence of IEDs separately in a waking state (WS) and sleeping state (SS) during FMP and RMP. In each period, patients were categorized as having unitemporal or bitemporal IEDs. Surgical outcome was classified at year 1 after surgery and at last follow-up visit as Engel I or Engel II—IV; and alternatively as completely seizure-free or not seizure-free.
Results: There were significant changes in relative IED lateralization between FMP and RMP during SS. The representation of patients with unitemporal IEDs declined from 37 (86%) in FMP during SS to 25 (58%) in RMP during SS ($p = 0.003$). At year 1 after surgery, the relative IED lateralization is a predictive factor for surgical outcome defined as Engel I vs. Engel II—IV in

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http://dx.doi.org/10.1016/j.eplepsyres.2014.06.009

both FMP during WS ($p = 0.037$) and during SS ($p = 0.007$), and for surgical outcome defined as completely seizure-free vs. not seizure-free in FMP during SS ($p = 0.042$). At last follow up visit, the relative IED lateralization is a predictor for outcome defined as Engel I vs. Engel II—IV in FMP during SS ($p = 0.020$), and for outcome defined as completely seizure-free vs. not seizure-free in both FMP during WS ($p = 0.043$) and in FMP during SS ($p = 0.015$). When stepwise logistic regression analysis was applied, only FMP during SS was found to be an independent predictor for surgical outcome at year 1 after surgery (completely seizure-free vs. not seizure-free $p = 0.032$, Engel I vs. Engel II—IV $p = 0.006$) and at last follow-up visit (completely seizure-free vs. not seizure-free $p = 0.024$, Engel I vs. Engel II—IV $p = 0.017$). Gender was found to be independent predictor for surgical efficacy at year 1 if the outcome was defined as completely seizure-free vs. not seizure-free ($p = 0.036$).

Conclusion: The predictive value of relative IED lateralization with respect to surgical outcome in interictal EEG is present only during FMP; the predictive value decreases with the reduction of AEDs caused by the change of relative IED lateralization.

Introduction

Temporal lobe epilepsy (TLE) is the most common form of drug-resistant epilepsy (Wiebe et al., 2001). Surgery was proved to be an effective therapeutic method in cases where pharmacological treatment failed (Williamson, 1998). In approximately two-thirds of patients, surgery leads to seizure freedom (Engel, 1996; Janszky et al., 2005a).

Many investigators focused on the evaluation of interictal EEG and its significance in predicting post-surgical outcome. In general, in patients with TLE, the relative lateralization of interictal epileptiform discharges (IEDs), i.e. the lateralization ratio of interictal spikes between the two hemispheres (unitemporal or bitemporal), appears to have prognostic value. Unitemporal IEDs are thought to be a favorable prognostic factor, while bitemporal IEDs are associated with worse outcomes (Chung et al., 1991; Radhakrishnan et al., 1998; Villanueva et al., 2004). This division fails in the subgroup of patients with mesial TLE associated with unilateral HS proved by histopathological examination or unilateral hippocampal atrophy on magnetic resonance imaging (MRI). Three studies focused on this subgroup proved no differences in surgical outcome between patients with unitemporal and bitemporal IEDs (Hardy et al., 2003; Janszky et al., 2005b; Krendl et al., 2008). Schulz et al. (2000) proved significant differences in outcome between these two groups, but their study included both mesial TLE associated with HS and non-lesional cases. Aull-Watschinger et al. (2008) found the relative IED lateralization to be a predictive factor for short-term (at year 1 and 2 after surgery) outcomes where an excellent outcome was defined as no seizures, with or without nondisabling auras, during the 12 month-period prior to the assessment, but there were no statistically significant differences between patients with unitemporal and bitemporal IED if the excellent outcome was defined as complete seizure freedom at any time after surgery.

Antiepileptic drug (AED) reduction influences neither the frequency of IEDs nor the localization of seizure origin, but the influence of AED reduction on relative IED lateralization has not yet been systematically studied (Gotman and Marciani, 1985; Gotman and Koffler, 1989; Marciani and Gotman, 1986; So and Gotman, 1990; Spencer et al., 1981).

The main goal of our study was to determine if there is a change in relative IED lateralization and/or interictal EEG prognostic value related to the surgical outcome caused by AED reduction and the effect of sleep in patients with mesial TLE associated with unilateral HS.

Methods

Patient selection

This retrospective study included all the patients with unilateral HS who had surgery at the Brno Epilepsy Center of St. Anne's University Hospital between 2005 and 2011 and who reached at least 1 year follow-up after the surgery. All included patients had unilateral HS on MRI, the presence of which was subsequently proven by histopathological evaluation. We excluded patients with other possible epileptogenic lesion than HS present on MRI, except blurring of border between gray and white matter in temporal pole and subsequently detected focal cortical dysplasia (FCD) in histopathological specimen of resected tissue of temporal pole. These criteria were applied because it seems that FCD in the temporal pole does not influence surgical outcome and because standard anteromedial temporal lobe resection was performed in all patients (Kuba et al., 2012)

We analyzed interictal EEG during semi-invasive video-EEG monitoring (scalp EEG + sphenoidal electrodes) in both waking state (WS) and sleeping state (SS). The SS analysis was performed in the non-rapid eye movement (non-REM) sleep stage II-III in two periods. These two periods were defined by AED daily dosage, as a full medication period (FMP) and a reduced medication period (RMP). Only patients with both WS and SS recordings during FMP as well as during RMP were included in this study (see below—EEG criteria) (Fig. 1).

Patient demographic data (age at seizure onset, epilepsy duration, age at time of surgery, time after surgery), other characteristics [number of habitual seizures per month, occurrence of habitual generalized tonic—clonic seizures (GTCS) in two years preceding surgery], and data describing semi-invasive EEG monitoring (duration and number of seizures) were assessed by reviewing patient charts.

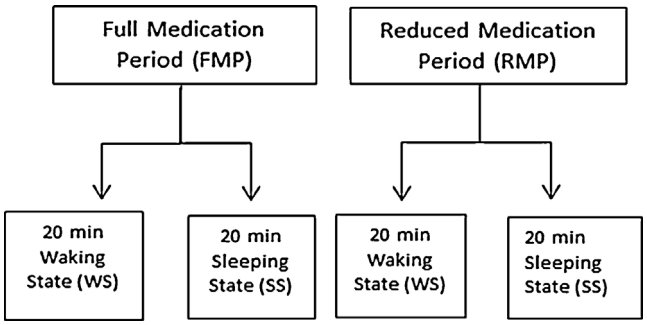

Fig. 1 The schema of interictal EEG evaluation during FMP and RMP. (FMP—full medication period, RMP—reduced medication period.)

We included a total of 43 patients who fulfilled these criteria. All patients gave their informed consent. The study was approved by the ethics committee of St. Anne's University Hospital.

Presurgical evaluation

All 43 patients underwent a comprehensive evaluation, including detailed history and neurological examination, neuropsychological testing, MRI, and semi-invasive video-EEG monitoring with sphenoidal electrodes. Fluorodeoxyglucose-positron emission tomography (FDG-PET) was performed in all patients; other functional neuroimaging techniques such as ictal SPECT and subtraction ictal SPECT co-registered to MRI (SISCOM) were performed in 15 patients out of 43 (35%) patients. Invasive EEG was additionally performed in 4 out of 43 (9%) patients, because their non-invasive data were found to be insufficiently conclusive to proceed directly to surgery.

EEG analysis

All patients were investigated using semi-invasive video-EEG monitoring. Semi-invasive EEG was recorded with the international 10—20 system with anterotemporal (T1, T2), supraorbital (SO1, SO2), and sphenoidal electrodes (Sp1, Sp2). The EEG recording was performed on the 64-channel Alien Deymed system. Monopolar recordings (a reference electrode on the mastoid process) and special bipolar montages were used to evaluate the EEG activity. EEG was amplified with a bandwidth of 0.4—70 Hz at a sampling rate of 128 Hz. The EEG was analyzed independently for the presence of IEDs by two authors of this study (ID and RK) both authors were blinded and discrepancies were resolved by consensus. IEDs were considered to be spikes, sharp waves, and spike-wave complexes. A spike or sharp wave had duration of <200 ms, was distinguished by its morphology and/or amplitude from normal background activity, and was usually followed by a slow wave.

Both FMP and RMP were characterized by the analysis of a 20-min WS and a 20-min SS interictal EEG recording sample (Fig. 1). These EEG samples were chosen from our archive, where interictal EEG specimens blindly selected by our technical staff from 24-h recordings are stored longterm (we do not store whole 24-h samples), on the basis of several criteria. First, interictal EEG analysis in FMP was always made without any antiepileptic drug (AEDs) reduction. Second, interictal EEG analysis in RMP was always made after at least 48 h after AED reduction initialization. The AED reduction velocity was individualized to the patient (depending on the frequency of habitual seizures, presence/absence of GTCS, etc.) on the basis of physician decision. We excluded the patients, in whom the AED reduction was not made. Third, the SS analysis was performed during non-REM sleep stages II—III; the minimal representation of stage III as the most important inductor of IED was 30% in a single SS recording (Malow et al., 1997; Sammaritano et al., 1991). The sleep stages were scored using the American Academy of Sleep Medicine Manual (Iber et al., 2007). Fourth, we did not include the EEG trace if (1) the recording was made 5 min before the seizure and/or 60 min after the seizure, (2) analysis was prevented by artifact, or (3) the recording duration was shorter than 20 min. The 5-min pre-seizure limit was chosen because no changes in spiking prior to seizures were found in previously published studies (Gotman and Marciani, 1985; Gotman and Koffler, 1989; Katz et al., 1992). The 60-min post-seizure limit was selected as sufficient for practical purposes, even though the changes following seizures can persist for hours and even days (Gotman and Marciani, 1985; Gotman and Koffler, 1989). Fifth, if more than one interictal EEG sample was available for analysis, we always chose the first one which fulfilled previously described criteria.

We described the relative lateralization of IEDs between the temporal lobe with HS (HS side) and the contralateral temporal lobe (non-HS side) by laterality index (LI). LI was defined as:

$$\mathrm{LI} = \frac{\text{IEDS on HS side} - \text{IEDS on non HS side}}{\text{IEDS on HS side} + \text{IEDS on non HS side}}$$

LI can range from 1 to −1. If the IEDs are all localized on the HS side, LI equals 1. If the IEDs are equally distributed between the HS side and non-HS side, LI equals 0. If the IEDs are all localized on the non-HS side, LI equals −1.

According to LI value, we divided our patients into two groups:

- unitemporal IEDs ($\mathrm{LI} \geq 0.8$)—the group of patients with strictly or predominantly unitemporal IEDs, i.e. more than 90% of IEDs localized on HS side
- bitemporal IEDs ($\mathrm{LI} < 0.8$)—the group of patients with independent bitemporal IEDs, i.e. less than 90% of IEDs localized on HS side.

The 90% cut-off value was based on the results of Chung et al. (1991), who proved that the patients with more than 90% of IEDs lateralized to the operated temporal lobe have comparable surgical results to the patients with strictly unitemporal IEDs.

Surgical procedure and outcome

Anteromedial temporal lobe resection was performed on all patients. Surgical efficacy was evaluated at regularly scheduled visits usually every 3 months, only in minority

Table 1 Patient demographic data and characteristics.

Demographic data		
Age at epilepsy onset in years (mean ± SD, ranges from-to)	12.6 ± 10.6	0.5—42
Duration of epilepsy in years (mean ± SD, ranges from-to)	26.3 ± 12.5	4—44
Age at time of surgery in years (mean ± SD, ranges from-to)	38.9 ± 9.4	19—56
Patients' characteristics		
The number of habitual seizures in a patient per month (median, ranges from-to)	5	1—30
The number of seizures in a patient during semi-invasive EEG (median, ranges from-to)	4	1—10
FCD in the temporal pole in histopathological specimen in number (%) of patients	7 (16)	

FCD—focal cortical dysplasia.

of patients the efficacy was reported by their neurologist in their place residence, and it was categorized according to Engel classification (Engel, 1987) and simultaneously according to the classification proposed by the International League Against Epilepsy (ILAE) (Wieser et al., 2001). Patients were categorized as Engel I (no seizures, with or without nondisabling auras, during the 12-month period prior to the assessment) or as Engel II—IV (Engel, 1987). They were then categorized as completely seizure-free (i.e. complete seizure freedom and absence of nondisabling auras at any time after surgery; correlates class Ia according to ILAE classification) or not seizure-free. For further analysis, two time milestones — year 1 after surgery, and last follow-up visit — was chosen because of the change of surgical responsiveness over time (Janszky et al., 2005b; Salanova et al., 1996).

Neuropathological examination

Evaluable formalin-fixed paraffin-embedded tissues of anterior temporal resection specimens including the hippocampal complex were available from all patients. The paraffin-embedded tissue specimens, slides, and histopathology reports were retrieved from the files of the First Department of Pathological Anatomy of St. Anne's University Hospital and re-evaluated by a histopathologist experienced in the evaluation of specimens obtained from epilepsy surgery patients (MH). All examined resected tissues were identically treated, fixed in 10% neutral buffered formalin, grossly inspected, carefully oriented, and measured. Temporal pole resection specimens were cut so as to obtain 2—3 mm thick tissue slices perpendicular to the cortical surface. Hippocampal *en block* resections were dissected into 2—3 mm thick tissue slices along the anterior-posterior axis. Representative tissue samples were routinely processed and paraffin embedded. Five μm thick tissue sections were stained by hematoxylin and eosin, evaluated under light microscope, and reported. NeuN immunohistochemistry (using mouse monoclonal anti-NeuN antibody, dilution 1:100, clone A-60, Millipore), was performed on preselected tissue sections if there was an inconclusive picture in hematoxylin and eosin. The classification system for HS reported by Blümcke et al. (2007) was applied. If FCD was present in the temporo-polar region, the classification system reported by Blümcke et al. (2011) was used.

Statistics

McNemar's test was used to test the LI change between FMP and RMP during both WS and SS. Fisher's exact test was applied to analyze the relation between LI and surgical outcome. The Mann—Whitney or Fisher's exact tests were used to analyze the relation between LI and patient demographic data and characteristics or data describing semi-invasive EEG monitoring. A univariate logistic regression analysis was applied to assess the influence of other variables (age at time of surgery, age at epilepsy onset, duration of epilepsy, time from surgery, sex, side of surgery, presence of FCD, frequency of habitual seizures, presence of habitual GTCS) on surgical outcome. Moreover, a stepwise logistic regression analysis using a forward selection procedure was performed to assess the independent influence of relative IED lateralization in FMP and RMP during WS and SS, and of patients' demographic data and characteristics on surgical outcome. The odds ratios were calculated and the Wald statistics applied to test whether the regression coefficients were statistically significantly different from zero. In all statistical tests, p-value <0.05 was considered to be statistically significant.

Results

Demographic data, surgery and outcome

The study included 43 patients: 21 females and 22 males. Patient demographic data and characteristics are summarized in Table 1.

Surgery was performed on the right side in 21 out of 43 (49%) patients and on the left side in 22 out of 43 (51%) patients. The duration of follow-up ranged from 1 to 8 years (with an average 4.5 ± 2.0 years). At year 1 after surgery, 35 out of 43 (81%) patients were classified as Engel I and 8 out of 43 (19%) as Engel II—IV (2 as Engel II, 2 as Engel III, and 4 as Engel IV). At this time milestone, 31 out of 43 (72%) were classified as completely seizure-free and 12 (28%) as not seizure-free. At the last follow-up visit using Engel's classification, 33 out of 43 (77%) patients were classified as Engel I and 10 out of 43 (23%) patients as Engel II—IV (3 as Engel II, 4 as Engel III, and 4 as Engel IV). At the last follow-up visit, 28 out of 43 (65%) patients were classified

Table 2 The relative IED distribution between HS side and non-HS side and its relation to surgical outcome at year 1 after surgery classified as Engel I or Engel II—IV during FMP and RMP for different LI values.

	FMP				RMP			
	WS		SS		WS		SS	
	uni IEDs	bi IEDs	uni IEDs	bi IEDs	uni IEDs	bi IEDs	uni IEDs	bi IEDs
Engel I *n* (%)	33 (87)	2 (40)	33 (89)	2 (33)	27 (84)	8 (73)	21 (84)	14 (78)
Engel II—IV n (%)	5 (13)	3 (60)	4 (11)	4 (67)	5 (16)	3 (27)	4 (16)	4 (22)
Total number	38	5	37	6	32	11	25	18
p-Value	$p = 0.037$		$p = 0.007$		$p = 0.401$		$p = 0.701$	

bi IEDs—bitemporal interictal epileptiform discharges, FMP—full medication period, uni IEDs—unitemporal interictal epileptiform discharges, RMP—reduced medication period, SS—sleeping state, WS—waking state.

as completely seizure-free and 15 out of 43 (35%) patients as not seizure-free.

AEDs treatment

At the time of semi-invasive EEG monitoring, monotherapy was used in 3 out of 43 (7%) patients; the other 40 out of 43 (93%) patients were treated with combinations of AEDs: 30 (70%) patients with a combination of two AEDs and 10 (23%) with a combination of three AEDs.

Interictal EEG during FMP was analyzed in all patients before the occurrence of seizures; 12 out of 43 (28%) patients exhibited seizures before EEG analysis in RMP. The other 31 out of 43 (82%) patients had seizures after the analysis of interictal EEG in RMP.

The relative IED lateralization between HS side and non-HS side

During FMP, 38 out of 43 (88%) patients had unitemporal IEDs in WS, the number of patients with unitemporal IEDs decreased to 37 (86%) in SS. During RMP, 32 out of 43 (74%) patients had unitemporal IEDs in WS in contrast to only 25 (58%) in SS. In all evaluated periods, 24 out of 43 (56%) patients had exclusively unitemporal IEDs, the other 19 out of 43 (44%) patients had bitemporal IEDs in at least one period. No patient had unitemporal IEDs in SS and simultaneously bitemporal IEDs in WS during either FMP or RMP.

When we evaluated the change in the relative IED lateralization between FMP and RMP, a significant difference was present in SS ($p = 0.003$) but not in WS ($p = 0.114$).

The change in relative IED lateralization during SS between FMP and RMP could have been caused in 12 patients with the occurrence of seizures preceding EEG analysis in RMP, therefore we also tested separately the change in relative IED lateralization between FMP and RMP in patients in whom the EEG analysis during RMP was not preceded by seizures ($n = 31$). In this smaller group, 27 out of 31 (87%) patients had unitemporal IEDs in FMP during WS, and 24 out of 31 (77%) patients in FMP during SS. During RMP, 27 out of 31 (87%) patients had unitemporal IEDs in WS, in contrast to 20 (65%) in SS. The difference in SS between FMP and RMP was significant even in this smaller group ($p = 0.023$).

Three out of 43 (7%) patients had independent extratemporal IEDs—the IEDs were present over ipsilateral central region in 1 patient, over ipsilateral frontal region in 1 patient, and over both frontal regions in 1 patient. Other analysis was not performed with extratemporal spikes because of small sample-size.

To conclude, there was a significant decrease in the number of patients with unitemporal IEDs in relation to AED reduction. This decline is present during sleep, but not in wakefulness, and is caused by activation of IEDs on the non-HS side.

Relative IED lateralization between HS side and non-HS side and surgical outcome at year 1 after surgery

At year 1 after surgery, relative IED lateralization has a predictive value for surgical outcome defined as Engel I vs. Engel II—IV in FMP during both WS and SS (Table 2). In FMP during WS, respectively, during SS, 33 out of 38 (87%), respectively, 33 out of 37 (89%) patients with unitemporal IEDs were classified as Engel I in comparison to 2 out of 5 (40%), respectively, 2 out of 6 (33%) patients with bitemporal IEDs ($p = 0.037$, respectively, $p = 0.007$). There were no differences in surgical outcome between patients with unitemporal IEDs and bitemporal IEDs in RMP during both WS and SS ($p = 0.401$; $p = 0.701$).

When patients were categorized according to ILAE classification as completely seizure-free and not seizure-free at year 1 after surgery, the statistical significant differences were found only in FMP during SS (Table 3). In FMP during SS, 29 out of 38 (78%) patients with unitemporal IEDs were categorized as completely seizure-free in comparison to 2 out of 6 (33%) patients with bitemporal IEDs ($p = 0.042$). There were no significant differences between patients with unitemporal IEDs and bitemporal IEDs in FMP during WS, and in RMP during both WS and SS ($p = 0.123$; $p = 1.000$; $p = 0.516$).

Relative IED lateralization between HS side and non-HS side and surgical outcome at last follow-up visit

Relative IED lateralization has a predictive value for surgical outcome defined as Engel I or Engel II—IV in FMP during SS (Table 4). During SS, 31 out of 38 (82%) patients with unitemporal IEDs were classified as Engel I in comparison to 2 out of 5 (33%) patients with bitemporal IEDs ($p = 0.020$). In FMP during WS, the results were borderline statistical

Table 3 The relative IED distribution between HS side and non-HS side and its relation to surgical outcome at year 1 after surgery classified as completely seizure-free or not seizure-free after surgery during FMP and RMP.

	FMP				RMP			
	WS		SS		WS		SS	
	uni IEDs	bi IEDs	uni IEDs	bi IEDs	uni IEDs	bi IEDs	uni IEDs	bi IEDs
CSF *n* (%)	29 (76)	2 (40)	29 (79)	2 (33)	23 (72)	8 (73)	19 (76)	12 (67)
NSF *n* (%)	9 (24)	3 (60)	8 (22)	4 (67)	9 (28)	3 (27)	6 (24)	6 (33)
Total number	38	5	37	6	32	11	25	18
p-Value	$p = 0.123$		$p = 0.042$		$p = 1.000$		$p = 0.516$	

bi IEDs—bitemporal interictal epileptiform discharges, CSF—completely seizure-free, FMP—full medication period, NSF—not seizure-free, RMP—reduced medication period, uni IEDs—unitemporal interictal epileptiform discharges, SS—sleeping state, WS—waking state.

Table 4 The relative IED distribution between HS side and non-HS side and its relation to surgical outcome at last follow-up visit classified as Engel I or Engel II-IV during FMP and RMP.

	FMP				RMP			
	WS		SS		WS		SS	
	uni IEDs	bi IEDs	uni IEDs	bi IEDs	uni IEDs	bi IEDs	uni IEDs	bi IEDs
Engel I *n* (%)	31 (82)	2 (40)	31 (84)	2 (33)	25 (78)	8 (73)	20 (80)	13 (72)
Engel II—IV *n* (%)	7 (18)	3 (60)	6 (16)	4 (67)	7 (22)	3 (27)	5 (20)	5 (28)
Total number	38	5	37	6	32	11	25	18
p-Value	$p = 0.073$		$p = 0.020$		$p = 0.698$		$p = 0.717$	

bi IEDs—bitemporal interictal epileptiform discharges, FMP—full medication period, uni IEDs—unitemporal interictal epileptiform discharges, RMP—reduced medication period, SS—sleeping state, WS—waking state.

non-significant ($p = 0.073$). There were no differences in surgical outcome between patients with unitemporal IEDs and bitemporal IEDs in RMP during both WS and SS ($p = 0.698$; $p = 0.717$).

When patients were classified as completely seizure-free or not seizure-free after surgery, we found a significant difference in relative IED lateralization in FMP during both WS and SS (Table 5). In FMP during WS, 27 out of 38 (71%) patients with unitemporal IEDs were categorized as completely seizure-free after surgery in comparison to 1 out of 5 (20%) patients with bitemporal IEDs ($p = 0.043$). Similarly, in FMP during SS, 27 out of 37 (73%) patients with unitemporal IEDs were completely seizure-free after surgery in comparison to 1 patient out of 6 (17%) with bitemporal IEDs ($p = 0.015$). We did not find any differences between these two groups in RMP during WS or SS.

Relative IED lateralization between HS side and non-HS side and other variables

No statistically significant differences were found according to relative IED lateralization in patient demographic data and characteristics or in data describing semi-invasive EEG (Table 6).

Surgical outcome and other variables

A univariate logistic regression analysis was performed to assess the influence of patients' demographic data or characteristics (age at time of surgery, age at epilepsy onset, duration of epilepsy, time from surgery, gender, side of surgery, presence of FCD, frequency of habitual seizures, presence of habitual GTCS), and relative IED lateralization in FMP and RMP during WS and SS on surgical outcome at year 1 after surgery (Table 7) and at last follow-up visit (Table 8).

To assess the independent influence of the previously mentioned variables on surgical outcome, a stepwise logistic regression was performed. According this stepwise logistic regression, only the relative IED lateralization in FMP during SS was found to be an independent predictor for surgical outcome at either year 1 after surgery (completely seizure-free vs. not seizure-free $p = 0.032$, Engel I vs. Engel II—IV $p = 0.006$) or at last follow-up visit (completely seizure-free vs. not seizure-free $p = 0.024$, Engel I vs. Engel II—IV $p = 0.017$). Gender was found to be independent predictor for surgical efficacy at year 1 if the outcome was defined as completely seizure-free vs. not seizure-free ($p = 0.036$).

Discussion

In our study, 44% of patients with TLE associated with HS exhibit bitemporal IEDs, defined by LI < 0.8, during semi-invasive video-EEG monitoring. These findings correlate well with results of previously published works. In studies focusing on the whole group of TLE, approximately 20—30% of patients were reported to have bitemporal IEDs (Chung et al., 1991; Radhakrishnan et al., 1998; Villanueva et al., 2004). In studies focusing on TLE associated with HS or unilateral hippocampal atrophy, the representation of patients

Table 5 The relative IED distribution between HS side and non-HS side and its relation to surgical outcome at last follow-up visit classified as completely seizure-free or not seizure-free after surgery during FMP and RMP.

	FMP				RMP			
	WS		SS		WS		SS	
	uni IEDs	bi IEDs	uni IEDs	bi IEDs	uni IEDs	bi IEDs	uni IEDs	bi IEDs
CSF *n* (%)	27 (71)	1 (20)	27 (73)	1 (17)	20 (63)	8 (73)	17 (68)	11 (61)
NSF *n* (%)	11 (29)	4 (80)	10 (27)	5 (83)	12 (37)	3 (27)	8 (32)	7 (39)
Total number	38	5	37	6	32	11	25	18
p-Value	$p = 0.043$		$p = 0.015$		$p = 0.719$		$p = 0.750$	

bi IEDs—bitemporal interictal epileptiform discharges, CSF—completely seizure-free, FMP—full medication period, NSF—not seizure-free, RMP—reduced medication period, uni IEDs—unitemporal interictal epileptiform discharges, SS—sleeping state, WS—waking state.

with bitemporal IEDs was higher; approximately 40% (Aull-Watschinger et al., 2008; Hardy et al., 2003; Krendl et al., 2008). The highest representation of bitemporal IEDs was reported by Ergene et al. (2000), who found them in approximately 60% of patients with non-lesional TLE during long-term EEG monitoring, although all patients in this study had only unitemporal IEDs on serial routine EEGs.

In our work, we found a change in relative IED lateralization during semi-invasive EEG monitoring that has not been previously described. The representation of patients with unitemporal IEDs declined between FMP and RMP from 88% to 74% in WS, and from 86% to 58% in SS, but only the difference in SS reached statistical significance. In our opinion, the change of relative IED lateralization between FMP and RMP in our study could be potentially conditioned by two factors: AED reduction and/or seizure occurrence. As we managed to prove significant changes in relative IED lateralization between FMP and RMP even in a subgroup of patients without seizures preceding RMP EEG analysis, we can assume that AED reduction could be sufficient to cause a relative IED lateralization change, but it seems that it needs the added effect of sleeping, which is generally accepted as a strong inductor of IEDs (Malow et al., 1997; Sammaritano et al., 1991).

As mentioned above, there are no studies focusing on the change of relative IED lateralization with respect to fast AEDs withdrawal during long-term EEG monitoring or seizure occurrence. Only two studies of the impact of fast AED reduction on IEDs have thus far been published, and both of them focused only on the change in IED frequency. AED reduction was found not to have any impact on IED frequency (Gotman and Marciani, 1985; Gotman and Koffler, 1989). IED frequency increase was related only to seizure occurrence followed them in hours and days in regions showing preictally the presence of IEDs and contemporary involved in seizure generation or propagation (Gotman and Marciani, 1985; Gotman and Koffler, 1989). It is necessary to point out that almost all the patients in these two studies had TLE; however, both studies used only invasive EEG and therefore their results may not apply for scalp or semi-invasive EEG. Moreover, minor IED frequency changes can cause significant changes in IED lateralization, and significant changes in IEDs frequency may not have any impact on IED lateralization. The incidence of patients with bitemporal IEDs increased during semi-invasive EEG monitoring; this change is substantial mainly during sleep, and even AED reduction is a sufficient causative factor.

Patients with unitemporal IEDs tend to have excellent prognosis within the whole group of TLE, i.e. within the group of TLE associated with different etiology (Chung et al., 1991; Radhakrishnan et al., 1998; Villanueva et al., 2004). In a study by Chung et al. (1991), 89% of patients with more than 90% of IEDs localized to the side of operation had good surgical outcomes (seizure free, or significant improvement), in comparison with 35% of patients with less than 90% of IEDs localized to the operated side. In a study by Radhakrishnan et al. (1998), patients with 100% of IEDs on the operated side had excellent outcomes (seizure freedom, or only no disabling seizures) in 74%, compared with 44% in those who had less than 100% of IEDs on operated side. In spite of these convincing findings within the group of TLE as a whole, the results about the prognostic value of IED lateralization in the subgroup of mesial TLE are more diverse (Aull-Watschinger et al., 2008; Hardy et al., 2003; Krendl et al., 2008; Schulz et al., 2000). Only Aull-Watschinger et al. (2008) and Schulz et al. (2000) proved significant differences in relation to relative IED lateralization. Aull-Watschinger et al. (2008) found unilateral IEDs to be associated with excellent short-term (i.e. at year 1 and 2 after surgery) outcome where this outcome was defined on the basis of Engel classification as no seizures, with or without nondisabling auras, during a 12 month-period prior to the assessment. The difference between patients with unitemporal and bitemporal IEDs was lost in long-term (i.e. at year 5 after surgery) follow-up, and when the definition of complete seizure-freedom (i.e. no seizures plus no auras at any time after surgery), which seems to be a more appropriate indicator of patient quality of life, was applied. In the study of Schulz et al. (2000), almost 85% of patients with strictly unilateral temporal IEDs are postoperatively categorized as completely seizure free, compared with 52% of patients with bilateral or ipsilateral extratemporal IEDs, but they included mesial TLE associated with HS and non-lesional cases. Hardy et al. (2003) found no significant difference in surgical outcome in 118 patients with HS in relation to IED lateralization. In their study, 65% of patients with ipsilateral temporal IEDs, 50% with ipsilateral temporal and simultaneous extratemporal IEDs, and 61% with bilateral IEDs were postoperatively seizure free. Janszky et al. (2005b) proved no statistically significant differences in short-term or in long-term surgical

Table 6 Differences between LI groups and demographic data, patient and semi-invasive EEG monitoring characteristics.

	FMP				RMP			
	WS		SS		WS		SS	
	uni IEDs	bi IEDs	uni IEDs	bi IEDs	uni IEDs	bi IEDs	uni IEDs	bi IEDs
Demographic data								
Mean age at epilepsy onset	12.2 ± 9.9	16.0 ± 16.0	12.0 ± 10	16.2 ± 14.3	11.4 ± 8.8	16.0 ± 14.7	11.9 ± 9.2	13.6 ± 12.4
p Value	*p* = 0.595		*p* = 0.390		*p* = 0.577		*p* = 0.941	
Mean duration of epilepsy	26.2 ± 12.5	27.0 ± 13.9	26.6 ± 12.4	24.5 ± 13.9	27.8 ± 12.2	21.7 ± 12.9	27.4 ± 12.3	24.7 ± 13.0
p Value	*p* = 0.835		*p* = 0.792		*p* = 0.159		*p* = 0.522	
Mean age at surgery	38.3 ± 9.0	43 ± 12.3	39.6 ± 9.0	40.1 ± 12.4	39.3 ± 9.1	37.7 ± 10.7	39.3 ± 8.8	38.3 ± 10.4
p Value	*p* = 0.255		*p* = 0.587		*p* = 0.717		*p* = 0.768	
Patients characteristic								
FCD *n*(%)	6 (16)	1 (20)	6 (16)	1 (17)	6 (19)	1 (9)	4 (16)	3 (17)
p Value	*p* = 1.000		*p* = 1.000		*p* = 0.656		*p* = 1.000	
Habitual seizure frequency								
≤5/month *n* (%)	30 (79)	3 (60)	30 (81)	3 (50)	24 (75)	9 (82)	19 (76)	14 (78)
>5/month *n* (%)	8 (21)	2 (40)	7 (19)	3 (50)	8 (25)	2 (18)	6 (24)	4 (22)
p Value	*p* = 0.575		*p* = 0.127		*p* = 0.575		*p* = 1.000	
Habitual GTCS in number (%) of patients	17 (45)	3 (60)	17 (46)	3 (50)	17 (53)	3 (27)	11 (44)	9 (50)
p Value	*p* = 0.650		*p* = 1.000		*p* = 0.175		*p* = 0.763	
Semi-invasive EEG								
Mean duration, days	6.0 ± 1.8	5.2 ± 1.8	6.0 ± 2.2	5.0 ± 1.7	5.9 ± 2.0	5.8 ± 2.6	6.1 ± 2.2	5.5 ± 2.2
p Value	*p* = 0.570		*p* = 0.318		p = 0.676		*p* = 0.680	
Number of seizures								
≤ 5 n(%)	33 (87)	5 (100)	32 (86)	6 (100)	27 (84)	11 (100)	21 (84)	17 (94)
>5 *n*(%)	5 (13)	0 (0)	5 (14)	0 (0)	5 (16)	0 (0)	4 (16)	1 (6)
p Value	*p* = 1.000		*p* = 1.000		p = 0.306		*p* = 0.380	

bi IEDs—bitemporal interictal epileptiform discharges, FCD—focal cortical dysplasia, FMP—full medication period, GTCS—generalized tonic clonic seizures, RMP—reduced medication period, SS—sleeping state, uni IEDs—unitemporal interictal epileptiform discharges, WS—waking state.

Table 7 The influence of demographic data and LI index on surgical outcome at year 1 after surgery defined as Engel I or Engel II-IV and as completely seizure-free or not seizure-free - results of the univariate logistic regression analysis.

Variable	Risk category/baseline category	Outcome—CSF vs. NSF		Outcome—Engel I vs. Engel II—IV	
		OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Gender	Male/female	4.75 (1.07—21.14)	0.041	4.00 (0.71—22.67)	0.117
Age at epilepsy onset	—	1.01 (0.95—1.08)	0.695	1.02 (0.96—1.10)	0.514
Duration of epilepsy	—	1.00 (0.95—1.06)	0.950	0.99 (0.93—1.05)	0.713
Age at surgery	—	1.02 (0.95—1.10)	0.601	1.01 (0.93—1.10)	0.803
Side of surgery	Right/left	1.07 (0.28—4.04)	0.924	1.06 (0.23—4.92)	0.942
FCD	Yes/no	1.04 (0.17—6.26)	0.966	0.69 (0.07—6.70)	0.749
Habitual seizure frequency	≤5/month/>5/month	1.74 (0.31—9.69)	0.528	0.89 (0.15—5.29)	0.897
Habitual GTCS	Yes/no	0.76 (0.20—2.93)	0.692	1.19 (0.26—5.52)	0.827
FMP—WS	bi IEDs/uni IEDs	4.83 (0.70—33.61)	0.111	9.90 (1.31—74.73)	0.026
FMP—SS	bi IEDs/uni IEDs	7.25 (1.12—47.00)	0.038	16.50 (2.26—120.64)	0.006
RMP—WS	bi IEDs/uni IEDs	0.96 (0.21—4.45)	0.957	2.02 (0.40—10.38)	0.397
RMP—SS	bi IEDs/uni IEDs	1.58 (0.41—6.06)	0.502	1.50 (0.32—7.01)	0.606

bi IED—bitemporal interictal epileptiform discharges, CSF—completely seizure-free, FCD—focal cortical dysplasia, FMP—full medication period, GTCS—generalized tonic clonic seizure, NSF—not seizure-free, RMP—reduced medication period, SS—sleeping state, WS—waking state, uni IED—unitemporal interictal epileptiform discharges.

outcomes (i.e. at year 0.5, 2, 3, and 5) related to relative IED lateralization in their study of 171 patients with HS. In the study by Krendl et al. (2008) focusing on mesial TLE associated with unilateral hippocampal atrophy, the relative lateralization of IEDs was not found to be surgical predictor; 71% of patients with unitemporal IEDs and 60% of patients with bitemporal IEDs were postoperatively seizure free. In our study, the relation between relative IED lateralization and excellent surgical outcome defined as both Engel I and completely seizure-free exists, but is present only in FMP; moreover, only FMP in SS was an independent outcome predictor when stepwise logistic regression model was applied.

The contradictory results of our study and studies by Aull-Watschinger et al. (2008), Hardy et al. (2003), Janszky et al. (2005b) and Krendl et al. (2008) could be explained by different study design. We analyzed separately 20 min of waking and 20 min of sleeping interictal EEG recordings during two periods defined by relative AED level withdrawal. Aull-Watschinger et al. (2008), Janszky et al. (2005b), and Krendl et al. (2008) evaluated 10, 2, and 5 min samples, respectively, every hour. Hardy et al. (2003) assessed long-term EEG monitoring, but did not specify the evaluation method more precisely in their article.

Table 8 The influence of demographic data and LI index on surgical outcome at last follow-up visit defined as Engel I or Engel II—IV and as completely seizure-free or not seizure-free—results of the univariate logistic regression analysis.

Variable	Risk category/baseline category	Outcome—CSF vs. NSF		Outcome—Engel I vs. Engel II—IV	
		OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Gender	Male/female	2.00 (0.56—7.16)	0.287	3.17 (0.69—14.46)	0.137
Age at epilepsy onset	—	1.01 (0.95—1.07)	0.686	1.02 (0.95—1.08)	0.647
Duration of epilepsy	—	1.00 (0.95—1.05)	0.989	1.01 (0.96—1.08)	0.624
Age at surgery	—	1.01 (0.95—1.07)	0.663	1.05 (0.97—1.14)	0.251
Time from surgery in years	—	1.08 (0.79—1.47)	0.639	1.12 (0.79—1.60)	0.518
Side of surgery	Right/left	1.32 (0.38—4.64)	0.666	1.80 (0.43—7.59)	0.423
FCD	Yes/no	0.71 (0.12—4.18)	0.703	1.40 (0.23—8.63)	0.717
Habitual seizure frequency	≤5/month/>5/month	1.33 (0.29—6.14)	0.712	0.63 (0.13—3.08)	0.566
Habitual GTCS	Yes/no	1.01 (0.29—3.55)	0.988	1.20 (0.29—4.95)	0.801
FMP—WS	bi IEDs/uni IEDs	9.82 (1.01—98.00)	0.049	6.64 (0.93—47.55)	0.059
FMP—SS	bi IEDs/uni IEDs	13.50 (1.40—130.19)	0.024	10.33 (1.53—69.73)	0.017
RMP—WS	bi IEDs/uni IEDs	0.63 (0.14—2.82)	0.541	1.34 (0.28—6.43)	0.715
RMP—SS	bi IEDs/uni IEDs	1.35 (0.38—4.80)	0.640	1.54 (0.37—6.38)	0.553

bi IED—bitemporal interictal epileptiform discharges CSF—completely seizure-free, FCD—focal cortical dysplasia, FMP—full medication period, GTCS—generalized tonic clonic seizure, NSF—not seizure-free, RMP—reduced medication period, SS—sleeping state, WS—waking state, uni IED—unitemporal interictal epileptiform discharges.

The interictal EEG evaluation seems to be the most reliable in sleeping, when AED reduction has not yet been initiated. During RMP, the differences between individual LI groups with respect to surgical outcome are lost because of the changes in relative IED lateralization described in the previous part of discussion.

In the literature, there are some discrepancies in the value of sleeping recordings. Sammaritano et al. (1991) believed that evaluating interictal EEG during waking or rapid eye movement (REM) sleep is more reliable than evaluating slow wave sleep. In contrast, Adachi et al. (1996) proved that sleep never produced new misleading (i.e. incorrectly lateralizing) information, which is in concurrence with the results of our study during FMP. In this period, only 1 patient with LI $\geq$ 0.8 in the waking state developed LI < 0.8 in the sleeping state, and in this patient, the change probably reflected bitemporal impairment, because the patient was postoperatively categorized as Engel III. During RMP, the situation was rather different: 22% of patients categorized as having waking state LI $\geq$ 0.8 developed sleeping state LI < 0.8. We could hypothesize that results of Adachi et al. (1996) reflect FMP rather than RMP, because they evaluated initial sleeping EEG, and at the beginning of EEG monitoring the AED reduction, if already started, is generally minimal.

Adachi et al. (1996) also published that IEDs during sleep could lead to correct lateralization in patients with bitemporal IEDs in waking state. In our study, there was no patient with bitemporal IEDs in WS and simultaneously unitemporal IEDs in SS. This difference is caused by a different cut-off value for defining bitemporal IEDs; we used a 90% cut-off value, and Adachi et al. (1996) used a 75% cut-off value.

Ergene et al. (2000) found that patients with bitemporal IEDs tend to have longer epilepsy duration, but this difference did not reach statistical significance. Janszky et al. (2003) published that patients with bitemporal IEDs have higher seizure frequency and later epilepsy onset. In our study, no dissimilarities between patients with unitemporal and bitemporal IEDs with respect to epilepsy duration, seizure frequency, age at epilepsy onset, or other demographic data, patient characteristics, or video EEG monitoring characteristics were present.

When focusing on other factors except LI which could be supposed to influence surgical outcome, we found only gender to be statistically significant predictor at year 1 after if the excellent outcome was defined on the basis of complete seizure-freedom. It is interesting that similar results were present in study of Aull-Watschinger et al. (2008), they found male gender to be the only predictor of postoperatively complete seizure-freedom at year 2 after surgery. The suggestion of male gender as a positive predictor for short-term outcome is difficult to interpret and should be tested in larger series of patients. A study by Janszky et al. (2005a) identified several distinct predictors for outcome at years 2, 3, and 5 after surgery. The following factors were associated with worse surgical outcome in an individual year: the presence of sGTCS and ictal dystonia at year 2, longer epilepsy duration and ictal dystonia at year 3, and longer epilepsy duration at year 5.

We see three basic limitations of our work. First, we described AED reduction only on the basis of relative daily dose reduction, not by serum levels. Second, only relatively short and preselected periods (80 min) were analyzed in each patient, which could influence our results. Third, we did not use EEG polysomnography, which would enable us to more precisely identify sleeping stages. On the other hand, neither AED serum level measuring nor EEG polysomnography are methods common in the daily praxis of epilepsy centers during video-EEG monitoring, and the main purpose of this work was to provide a helpful tool for clinicians, both epileptologists and neurophysiologists, in patient evaluation. It is a challenge to perform an analogous prospective study with more detailed patient investigations, including AED serum levels, and 5 or 10 min samples every hour, or may be better continuous 24-h lasting interictal EEG evaluation. With respect to our conclusions, it would be meaningful to establish a cut-off value of AED reduction determining the change in relative IED lateralization. We were not able to find such cut-off value because in each individual patient we used only two recordings—one with full AED medication and one with marked AED reduction.

Conclusion

The relative IED lateralization in interictal EEG in patients with TLE with HS could be a predictor for surgical outcome, defined as both Engel I or Engel II—IV, and seizure-free or not seizure-free, only before initialization of AED reduction. Its predictive value is diminished with AED reduction because of changes in relative IED lateralization.

Acknowledgments

We thank Anne Johnson for grammatical assistance. This work was supported by the project ''CEITEC—Central European Institute of Technology'' (CZ.1.05/1.1.00/02.0068) from European Regional Development Fund.

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Annex 2: Frauscher B, von Ellenrieder N, Zelmann R, **Dolezalova I**, Minotti L, Olivier A, Hall J, Hoffmann D, Nguyen DK, Kahane P, Dubeau F, Gotman J. Atlas of the normal intracranial electroencephalogram: neurophysiological awake activity in different cortical areas. Brain. 2018;141:4.

doi:10.1093/brain/awy035 BRAIN 2018: 141; 1130–1144 | 1130

BRAIN
A JOURNAL OF NEUROLOGY

Atlas of the normal intracranial electroencephalogram: neurophysiological awake activity in different cortical areas

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In contrast to scalp EEG, our knowledge of the normal physiological intracranial EEG activity is scarce. This multicentre study provides an atlas of normal intracranial EEG of the human brain during wakefulness. Here we present the results of power spectra analysis during wakefulness. Intracranial electrodes are placed in or on the brain of epilepsy patients when candidates for surgical treatment and non-invasive approaches failed to sufficiently localize the epileptic focus. Electrode contacts are usually in cortical regions showing epileptic activity, but some are placed in normal regions, at distance from the epileptogenic zone or lesion. Intracranial EEG channels defined using strict criteria as very likely to be in healthy brain regions were selected from three tertiary epilepsy centres. All contacts were localized in a common stereotactic space allowing the accumulation and superposition of results from many subjects. Sixty-second artefact-free sections during wakefulness were selected. Power spectra were calculated for 38 brain regions, and compared to a set of channels with no spectral peaks in order to identify significant peaks in the different regions. A total of 1785 channels with normal brain activity from 106 patients were identified. There were on average 2.7 channels per cm^3 of cortical grey matter. The number of contacts per brain region averaged 47 (range 6–178). We found significant differences in the spectral density distributions across the different brain lobes, with beta activity in the frontal lobe (20–24 Hz), a clear alpha peak in the occipital lobe (9.25–10.25 Hz), intermediate alpha (8.25–9.25 Hz) and beta (17–20 Hz) frequencies in the parietal lobe, and lower alpha (7.75–8.25 Hz) and delta (0.75–2.25 Hz) peaks in the temporal lobe. Some cortical regions showed a specific electrophysiological signature: peaks present in $>60\%$ of channels were found in the precentral gyrus (lateral: peak frequency range, 20–24 Hz; mesial: 24–30 Hz), opercular part of the inferior frontal gyrus (20–24 Hz), cuneus (7.75–8.75 Hz), and hippocampus (0.75–1.25 Hz). Eight per cent of all analysed channels had more than one spectral peak; these channels were mostly recording from sensory and motor regions. Alpha activity was not present throughout the occipital lobe, and some cortical regions showed peaks in delta activity during wakefulness. This is the first atlas of normal intracranial EEG activity; it includes dense coverage of all cortical regions in a common stereotactic space, enabling direct comparisons of EEG across subjects. This atlas provides a normative baseline against which clinical EEGs and experimental results can be compared. It is provided as an open web resource (https://mni-open-ieegatlas.research.mcgill.ca).

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Received August 24, 2017. Revised November 30, 2017. Accepted January 1, 2018. Advance Access publication March 1, 2018

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Keywords: stereo-encephalography; physiology; spectral analysis; human; brain

Introduction

The scalp EEG during wakefulness in healthy individuals is well defined (Chang *et al*., 2011), but the knowledge accumulated on normal physiological intracranial EEG activity outside of the context of intracranial event-related potentials, task-related responses or intracranial stimulation (Jerbi *et al*., 2009; David *et al*., 2013; Matsumoto *et al*., 2017) is surprisingly scarce. This contrasts with the vast literature on epileptic activity in intracranial EEG (for a review see Frauscher and Dubeau, 2018). The knowledge of physiological intracranial EEG activity is based mainly on studies performed in the pre-MRI era using visual analysis of the recorded signals (Gastaut 1949; Jasper and Penfield, 1949; Petersen *et al*., 1953; Sem-Jacobsen *et al*., 1953, 1955, 1956; Chatrian *et al*., 1960 *a*, *b*; Ribstein, 1960; Perez-Borja *et al*., 1962; Graf *et al*., 1984). Evidence suggests that normal alpha, beta and gamma rhythms, and slow wave activity in the theta and delta range are observed in the intracranial EEG following a spatially distributed pattern. For instance, alpha rhythm was described in the occipital lobe, the parietal lobe just posterior to the postcentral gyrus, and the posterior temporal neocortex (Gastaut, 1949; Jasper and Penfield, 1949; Sem-Jacobsen *et al*., 1953, 1956; Chatrian *et al*., 1960*a*; Perez-Borja *et al*., 1962), and non-reactive alpha activity was found in the frontal lateral neocortex (Jasper and Penfield, 1949). Beta rhythm is most frequently seen over the anterior head regions. In particular, well sustained beta frequencies of ~25 Hz are described in the precentral and postcentral gyri with lower frequencies present in the postcentral region (Jasper and Penfield, 1949). Other normal activities such as mu rhythm (Graf *et al*., 1984) and lambda waves (Chatrian *et al*., 1960*a*, *b*; Perez-Borja *et al*., 1962; Chatrian, 1976) have also been described.

Location-related differences in the occurrence of these rhythms and patterns remain purely descriptive without attempts to determine the exact localization of the positions of the electrode contacts in a common space. Furthermore, quantitative studies of normal activity during resting wakefulness are either lacking or are restricted to certain brain areas, often with small patient numbers. The best evidence exists for the hippocampus where an activity in the theta delta range has been described in quiet wakefulness (Brazier, 1968; Huh *et al*., 1990; Meador *et al*., 1991; Nishida *et al*., 2004; Moroni *et al*., 2012). In an attempt to create an atlas of normal human brain activity during wakefulness, Kahane (1993) described the quantitative EEG distribution across several cortical areas using intracranial EEG performed in epilepsy patients during presurgical epilepsy work-up. Coordinates of the individual electrode positions were given in Talairach space. In this work, the author already highlighted the methodological difficulties to determine normality in an epileptic brain.

Patients with refractory focal epilepsies are the only human subjects where extensive intracranial cortical EEG studies are undertaken, and thus allow access not only to pathological but also to normal brain neurophysiology. We have a poor knowledge of the normative electrophysiological data of brain activity. This is explained by the relatively rare placement of electrodes in healthy brain tissue and the challenge in identifying healthy brain regions, and by the difficulty of standardization of the electrode placement compared to scalp EEG, resulting in problems performing interindividual comparisons of EEG patterns (each patient has at most a few contacts in healthy brain, with great variability in electrode location from patient to patient). Moreover, even in large tertiary epilepsy centres, only a small proportion of patients (~15–25 patients) are explored each year with intracranial electrodes.

The current work is a multicentre study aiming to provide an atlas of normal intracranial EEG activity recorded with both stereo-EEG electrodes and cortical grids/strips. These data are provided as an open web resource (https://mni-open-ieegatlas.research.mcgill.ca) developed under the LORIS framework (Das *et al*., 2016). Localization of the contacts in a common stereotactic space allows the accumulation and superposition of results from a large number of subjects and a direct comparison of EEG activity across subjects. The results of power spectra analysis during wakefulness are presented in this paper.

Materials and methods

Selection of intracranial EEG recordings

Charts and recordings of patients who underwent intracranial EEG investigation as part of their clinical evaluation for epilepsy surgery at the Montreal Neurological Institute and Hospital (MNI), Centre Hospitalier de l'Université de Montréal (CHUM), and Grenoble-Alpes University Hospital (CHUGA) were screened, starting with the most recent patients at time of data collection (September 2015 for MNI and CHUM, April 2016 for CHUGA), and moving consecutively

backward to January 2010 or earlier, to identify cases with <40 recordings fulfilling selection criteria.

Recordings of patients included for this study had to fulfil the following four inclusion criteria:

(i) presence of at least one channel with normal activity. Such channels are not common (on average 11% of channels per patient as shown in one of our previous studies) (Frauscher *et al.*, 2015). A channel with normal activity is defined as a channel localized in normal tissue as assessed by MRI, is located outside the seizure onset zone, does not show at any time of the circadian cycle interictal epileptic discharges (according to the clinical report of the complete implantation and to a careful investigation of one night of sleep by a board-certified electrophysiologist), and shows the absence of overt slow-wave anomaly;

(ii) presence of peri-implantation imaging (CT or MRI) for exact localization of individual electrode contacts (contacts located in the white matter were excluded);

(iii) availability of a controlled intracranial EEG recording obtained after a minimum of 72 h after insertion of stereo-EEG electrodes or 1 week after placement of subdural grids or strips (medications are usually not yet lowered), and at least 12 h after a generalized tonic-clonic seizure, 6 h in case of focal clinical seizures, or 2 h in case of purely electrographic seizures, and not after electrical stimulation, as done in our previous work (Frauscher *et al.*, 2015); and

(iv) sampling frequency of a minimum of 200 Hz. This minimum sampling frequency was chosen to include as many patients as possible for the analysis of frequencies in the classical Berger frequency bands (0.3–70 Hz).

The data collected in the three centres complemented each other well, as different implantation strategies are used (stereo-EEG electrodes versus subdural grids/strips, and frame-assisted versus frameless electrode placement), and provide a broad coverage of different cortical regions. Ethical approval was granted at the MNI as lead ethics organization (REB vote: MUHC-15-950).

Co-registration and anatomical localization of electrodes and electrode contacts

Registration to stereotaxic space and anatomical localization of electrodes was performed using minctools (www.bic.mni.mcgill.ca/ServicesSoftware/Services SoftwareMincToolKit) and the IBIS framework (Drouin *et al.*, 2017). Peri-implantation CT/MRI images showing electrode positions were linearly registered to pre-implantation MRI images (preMRI) of each patient. In turn, preMRIs were non-linearly registered to the ICBM152 2009c non-linear symmetric brain model (Mazziotta *et al.*, 2001; Fonov *et al.*, 2011). The combined transformation allowed estimation of the electrode positions in a common stereotaxic space in order to visualize the standardized atlas of normal EEG activity.

Anatomical structures were fully automatically segmented. We used an atlas created with an unbiased method (Fonov *et al.*, 2011) from manually segmented data of 20 normal subjects (Landman and Warfield, 2012). It consists of 132 grey matter labels (66 per hemisphere after excluding basal ganglia, cerebellum, midbrain and brainstem). We chose this atlas because it was detailed and contains deep as well as surface cortical regions. The preMRI was non-linearly registered to the atlas' averaged MRI and then the inverse transformation was applied to warp the labels back to the patient's space. In case of lesional epilepsy, segmentations were checked visually by an epileptologist in order to ensure that selected electrode contacts are indeed outside of lesional tissue. Patients with large cortical malformations such as extended polymicrogyria, hemimegalencephaly, agenesis of corpus callosum, or extended encephalomalacic lesions were excluded.

Each bipolar channel was represented by a volume made of a cylinder of length equal to the distance between its two electrode contacts, 10 mm diameter and one half sphere at each end. The anatomical localization of each channel was estimated by assessing in which segmented grey matter region laid the majority of its volume. The findings were grouped according to the topographical localization of the channels and plotted onto the standard ICBM152 template.

Selection of EEG sections

We visually selected 60 s sections (either continuous or consecutive discontinuous >5 s segments after artefact exclusion; 5 s were chosen as a compromise between minimizing the number of segments and obtaining the 60 s sections) of resting wakefulness EEG with eyes closed recorded during standardized conditions. The controlled 'eyes closed and eyes opened' recordings were part of the controlled intracranial EEG evaluation at the three participating sites. Analysis of EEG activity of the non-epileptic physiological channels was performed using Matlab (Mathworks). The signals were bandpass filtered at 0.5–80 Hz and downsampled to 200 samples per second if the original sampling rate was higher (original sampling rates were 200, 256, 512, 1000, 1024, and 2000 samples per second).

Analysis of the oscillatory component of the signal

The spectral density in each channel was estimated with Welch's method, i.e. averaging the magnitude of the discrete time Fourier transform of 59 overlapping blocks of 2 s duration and 1 s step, weighted by a Hamming window. In each channel the resulting spectral density was normalized to a total power equal to one, making it independent of the EEG signal amplitude.

To determine the presence of peaks in the spectrum, we first defined the 'no-peak set' as a set of channels with no peak in their spectrum. We defined this set in a data-driven procedure. The normalized spectra were classified into k-groups using the k-means algorithm, with 160 features given by the values at each frequency step (0.5 Hz steps between 0.5 and 80 Hz), Euclidean distance, and 100 repetitions. This separated channels according to their most prominent peaks in their spectrum. By repeating the classification with increasing number of groups k, eventually a group without peaks was found. We determined the presence of this group by requiring that its mean normalized spectrum be lower than the maximum among the other groups. From this group, we took the 50% of the channels closest to its mean to define the no-peak set.

Because as the frequency increases, the spectrum becomes more correlated between equally spaced frequency steps, we defined a set of unequal frequency intervals in which to test

for the presence of peaks in the spectrum. The intervals were selected so that each of them had at least 4% of the power of the average normalized spectrum of all the studied channels. This resulted in 22 frequency intervals (0.5–0.75–1.25–1.75–2.25–3.25–3.75–4.25–5.25–6.25–6.75–7.75–8.25–9.25–10.25–11.75–13.25–15.25–17.25–20.25–24.25–31.75–80 Hz). The presence of a peak at a given frequency interval in any particular brain region was determined by comparing the distribution of the normalized spectra of all the channels in the region at the desired frequency interval, to the distribution of the no-peak set at the same frequency interval. A one-sided two-sample Kolmogorov-Smirnov test was used, at 5% significance level with Dunnett's correction for multiple comparisons (for the number of tested anatomical regions times the number of frequency intervals). The two-sample Kolmogorov-Smirnov test is sensitive to differences in location and shape of the empirical cumulative distribution functions. A second test was performed for brain regions and frequency intervals in which significant differences were found, to determine the percentage of channels in the brain region of interest that had a significantly higher relative power than the no-peak set at the given frequency interval. We performed an uncorrected one-sided Wilcoxon rank-sum test (at 5% significance level), comparing the distribution of the no-peak set to the spectral density of each individual channel.

Analysis of the non-oscillatory component of the signal

To investigate the non-oscillatory component of the spectrum, we explored the scale-free dynamics of the brain activity by fitting a $1/f^{\beta}$ model to the high frequency end of the spectrum. We adapted the methodology used in previous studies (Yamamoto and Hughson, 1993; He *et al.*, 2010). We used non-overlapping Hamming windows of 1 s duration for the computation of the spectrum of the scale-free activity, and fitted the β coefficient in the 10–40 Hz range. We adopted a low end of 10 Hz instead of 1 Hz as in He *et al.* (2010), because we observed that in most of the channels the scale-free component of the spectrum had a shoulder between 1 and 10 Hz. The upper end of the range (40 Hz) is limited by the sampling rate of our data (the highest frequency not affected by the antialiasing down sampling filters is 80 Hz, but the computation of the scale-free component of the spectrum is correct only up to half this frequency). To determine if some regions had a different β coefficient, we computed the median value of β and performed a permutation test (100 000 permutations of region labels, Bonferroni corrected for 38 regions).

For exploring the nested frequencies in the brain activity, we performed a phase-amplitude coupling analysis. We computed the modulation index (Tort *et al.*, 2008) for phases at frequencies between 0.5 and 12 Hz, with 0.5 Hz steps. We explored the coupling to amplitude in 17 frequency bands (4–5–6–7–8–10–12–14–16–20–24–30–36–42–48, 52–58, 62–70–80 Hz). For computation of the modulation index we used eight phase bins. The Hilbert transform was implemented between 0.5 and 80 Hz, with an FIR filter of order 200. The bandpass filters were elliptic IIR filters of order 6 applied in two passes to achieve zero-phase. To determine the statistical significance of the observed modulation index, a set of 1000 surrogate amplitude signals were analysed for each channel, by partitioning the original time series in eight sections of random length and shuffling them. The mean and standard deviation (SD) of these surrogate data were used to determine the z-score of the modulation index. The proportion of channels with significant modulation index at different phase-frequency bins was computed, and a permutation test was performed to determine regional differences (100 000 permutations of region labels, Bonferroni corrected for 24×17 phase-frequency bins).

Results

Here we report on the cortical coverage for this project, the different electrode types used, as well as the automatic classification of the no-peak set, which is used subsequently to test for the presence of peaks in the spectrum of channels from different brain regions. We then describe the lobar differences in spectral density distribution, highlight the intracranial EEG signature of some cortical brain regions, stress unexpected findings, and analyse the non-oscillatory component of the signal.

Demographical information of the study sample

The study sample consisted of 106 patients (54 males; CHUGA: 49 patients, MNI: 40, CHUM: 17) with therapy-refractory focal epilepsy who underwent invasive intracranial EEG investigation during presurgical epilepsy work-up. The mean age was 33.1 ± 10.8 years. Eighty-nine patients (84%) were investigated with stereo-EEG electrodes, and 17 (16%) with grids/strips. Of the patients who were explored with grids/strips, all but two had additional stereo-EEG electrodes for exploring deep structures such as the insula or the mesiotemporal lobe.

Number and density of cortical channels with normal EEG activity

A total of 1785 intracranial EEG channels (left hemisphere, 1066; right hemisphere, 719) recording presumably normal physiological brain activity were identified. The positions of the investigated channels after co-registration in stereotaxic space are given in Fig. 1. There were on average 0.9 channels per cm^2 of cortical surface, and 2.7 channels per cm^3 of cortical grey matter volume. Restricting the channels to have an equal number of channels per region in both hemispheres (695 channels), we found no differences in the distribution of normalized spectral density between the channels from homologous regions of both hemispheres (two-sided two-sample Kolmogorov-Smirnov test with Dunnett's correction for 22 comparisons for the tested frequency intervals). Therefore, we grouped left and right hemisphere channels together. The figures show all channel positions flipped to one of the hemispheres of the symmetric atlas.

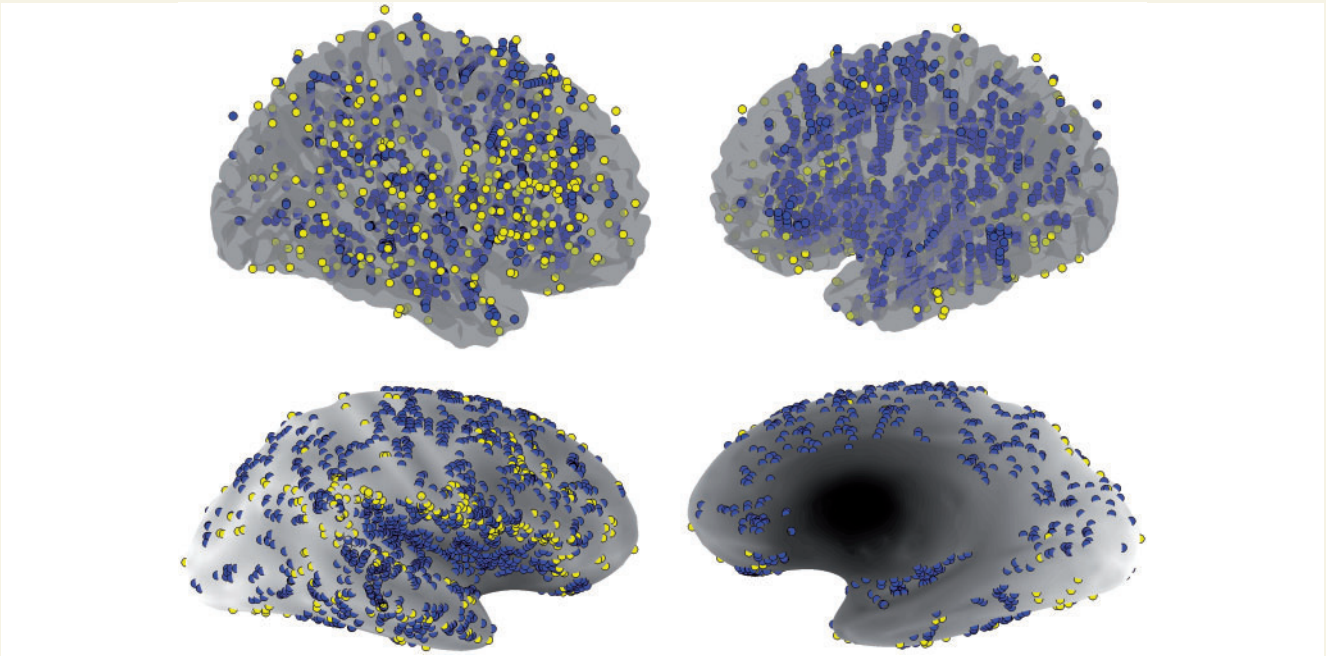

Figure 1 Localization of the 1785 EEG channels with normal physiological activity analysed for this study. The 1520 channels from stereo-EEG electrodes are visualized in blue, and the 265 channels from cortical grids and strips are in yellow. Note that for the 'inflated' brain display at the bottom, the electrodes are projected on the cortical surface.

The spectral density is similar in stereo-EEG electrodes and cortical grids/strips

Eighty-five per cent of the 1785 channels (1520) were from stereo-EEG electrodes, and 15% (265) from cortical grids and strips (Fig. 1). To compare the spatial coverage achieved with intracerebral electrodes and with cortical grids and strips we classified the cortical surface according to curvature, and compared regions with convex curvature (likely gyri) to regions of concave curvature (likely sulci). We found that grid channels were 5.3-times more frequent in the former, and stereo-EEG electrode channels 1.6-times more frequent in the latter (180 versus 34 and 412 versus 673 in convex versus concave regions, respectively; the remaining channels were in regions with no clear dominant curvature). This indicates that channels from cortical grids/strips are typically placed atop of gyri, and that stereo-EEG electrodes record not only from the sulci, but also from a significant fraction of the gyri. The normalized spectral density of the neocortical channels recorded with stereo-EEG (commercial DIXI electrodes, home-made MNI electrodes, or Ad-Tech electrodes) or cortical grids/strips (Ad-Tech electrodes) is similar across electrode types (Fig. 2A).

Interestingly, there is a ~2-fold increase in absolute amplitude (root mean square) in channels from cortical grids/strips compared to stereo-EEG electrodes (Fig. 2B). The difference is maintained when only neocortical channels are analysed (i.e. excluding mesiotemporal lobe structures). This difference does not affect subsequent results, as normalized spectra are used.

Automatic classification of channels and no-peak set

The procedure to separate a set of channels with no peaks in the spectrum from sets of channels with various peaks resulted in eight channel groups (no peak, one group and various peaks, seven groups). The median normalized spectral density of the groups can be observed in Fig. 3A, and the groups with spectral peaks correspond to peaks in the low delta band, high delta band, theta band, alpha band, low beta band, high beta band, and gamma band. Channels with delta or gamma activity usually do not show sustained rhythms, but simply an increase in the low or high frequency activity. The spectral density of what we define as 'the no-peak set', derived from the group of channels with no peak in their spectrum, is shown in Fig. 3B. This no-peak set is used in subsequent sections to test for the presence of peaks in the spectrum of channels from different brain regions. Figure 3C and D shows the distribution of the groups in the inflated cortex. Note that even though the frequency resolution of this unsupervised classification is poor, it shows a frequency increase from the posterior to the anterior cortical regions.

Lobar frequency differences in intracranial EEG

Figure 4 shows the difference in the spectral density of the standard EEG frequencies across the different brain lobes (758 frontal channels, 415 temporal, 355 parietal, and 105 occipital). The occipital lobe shows, as expected, a clear peak in alpha activity (significant in the 7.75–10.25 Hz, in

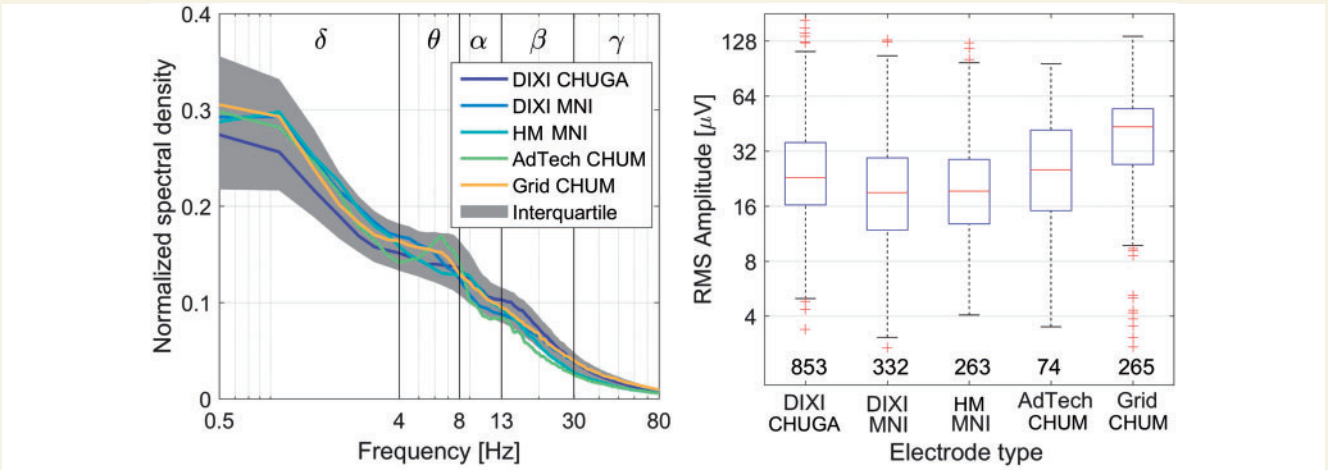

Figure 2 Comparison of different electrode types (stereo-EEG electrode types: DIXI CHUGA, DIXI MNI, MNI MNI, AdTech CHUM, and grids: CHUM). (**A**) Median spectral density for each electrode type. (**B**) Signal amplitude (and number of channels) according to electrode type and centre. Note the ~100% increase in absolute amplitude (root mean square, RMS) in channels from cortical grids/strips compared to stereo-EEG electrodes. CHUGA = Centre hospitalier de l'université de Grenoble-Alpes; CHUM = Centre hospitalier de l'université de Montréal; MNI = Montreal Neurological Institute.

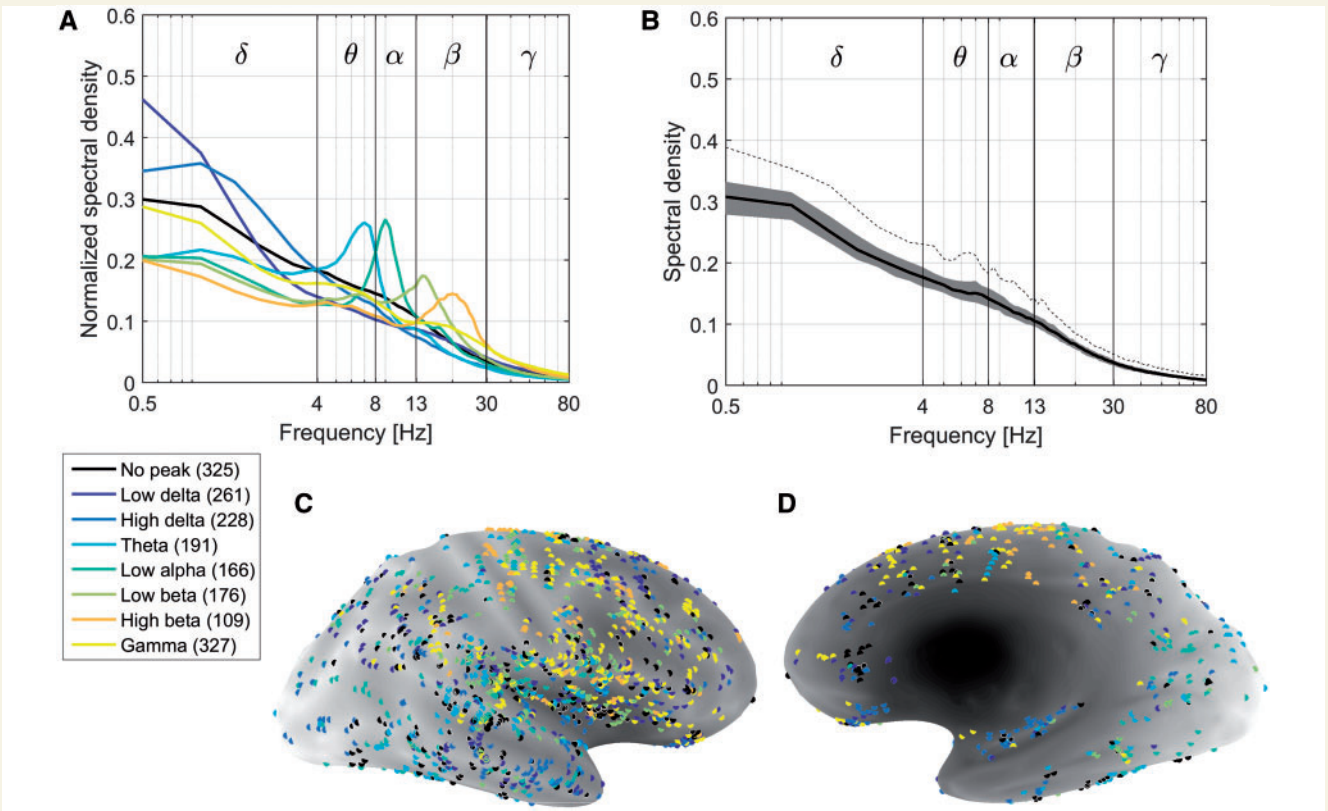

Figure 3 Unsupervised classification of channels and no-peak set. (**A**) Median normalized spectral density of the eight different groups obtained by the classification. Channels with delta or gamma activity usually do not show sustained rhythms (no peaks), but simply an increase in the low or high frequency activity. (**B**) The spectral density of the no-peak set, derived from the group of channels with no peak in their spectrum. (**C** and **D**) Distribution of the groups in the inflated cortex (lateral and mesial views). Even though the frequency resolution of this unsupervised classification is poor, the figure gives a rough global idea of the distribution of rhythms in the brain, and shows a posterior to anterior gradient of increasing frequencies.

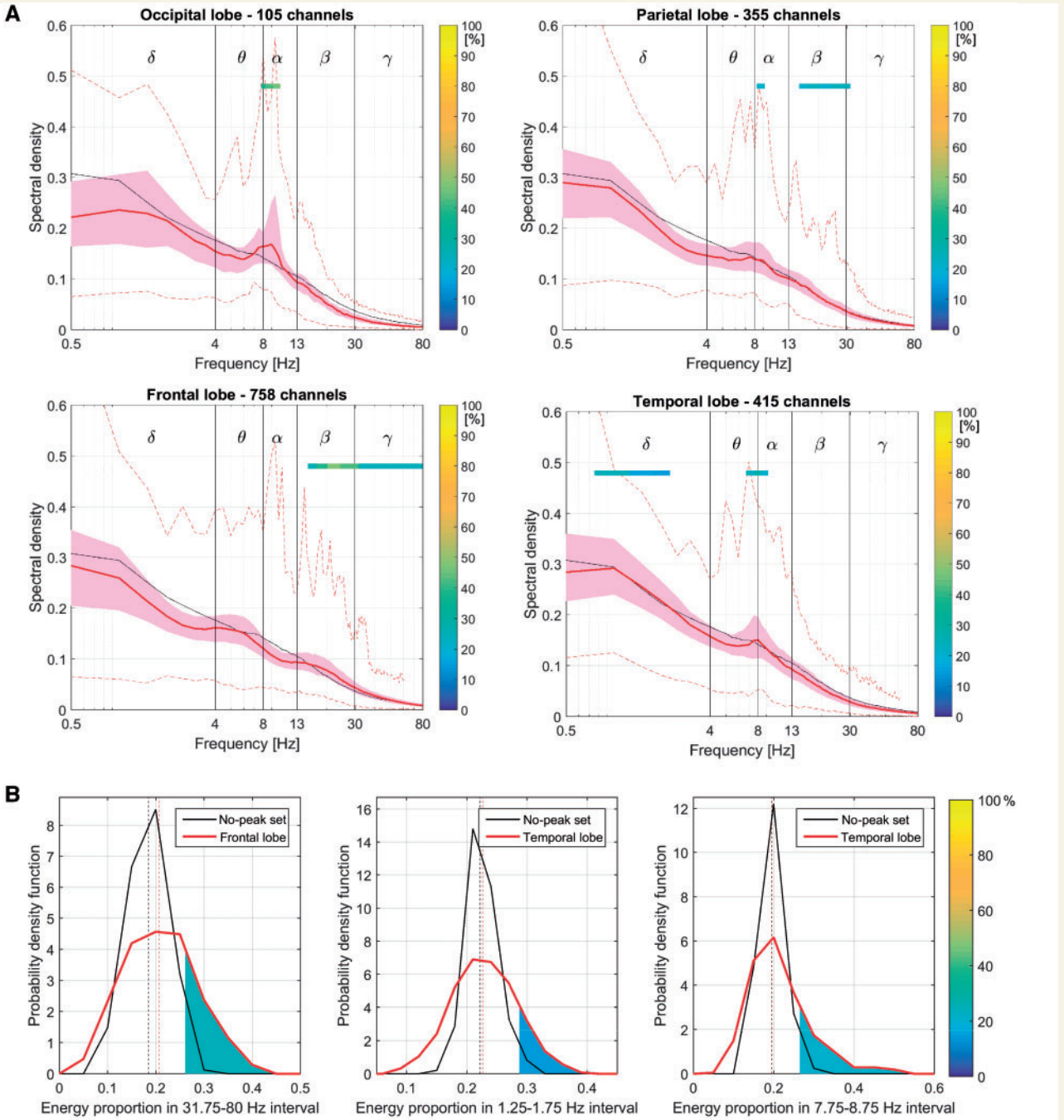

Figure 4 Lobar differences in EEG frequences. (**A**) Spectra of the different brain lobes in semi-logarithmic graph. The red line corresponds to the median spectral density of all the channels in the region. The 25 and 75 percentiles are indicated by the pink shaded region. The broken red lines show the upper and lower bounds of the spectral distribution at every frequency. The thin black line shows the median spectrum of the no-peak set used to determine the presence of peaks. Vertical black lines separate the common clinical frequency bands indicated by Greek letters. The coloured horizontal segments in the upper part of each graph indicate the presence of peaks. If the segment is present, it indicates that the distribution of the channel spectral densities is significantly higher than the distribution of the no-peak set. The colour of the line indicates the percentage of channels that have a significant deviation compared to the no-peak set at each frequency. (**B**) Illustration of differences not clearly visible in **A**. Each panel shows in black the distribution of the energy in the no-peak set for the given frequency interval, and the red line shows the distribution in different brain regions (frontal lobe and temporal lobe). The broken vertical lines indicate the median value, and the coloured area under the curve indicates the percentage of channels that has significantly higher power than the no-peak set in the corresponding frequency interval. The figure illustrates situations in which the test can find differences, not always obvious looking only at the median (in **A**). *Left*: Different position (mean, median) in the gamma band of the frontal lobe. *Middle*: Equal median but different dispersion (SD) in the delta band of the temporal lobe. *Right*: Equal median but asymmetric distribution (skewness) in the alpha band of the temporal lobe.

47% of the channels at ~10 Hz), whereas faster activity peaks in the beta and gamma band were recorded in the frontal lobe (16.75–80 Hz, in 48% of the channels at ~24 Hz). The parietal lobe shows peaks at intermediate frequencies in the alpha (8.75–9.75 Hz, in 21% of the channels) as well as in the beta band (16.75–31.75 Hz, in 24% of the channels at ~20 and 31.5 Hz). The temporal lobe shows a borderline alpha peak (7.25–9.25 Hz, in 30% of the channels at ~8 Hz), and some channels show a peak in delta activity (0.75–2.25 Hz, in 24% of the channels at ~1 Hz). Figure 4B shows the difference in the distribution for some of these cases, in which the difference is not clearly appreciated by looking at the median spectral density in Fig. 4A.

Some cortical brain regions have a specific EEG signature

We analysed the spectrum of channels in different anatomical brain regions. Some neighbouring anatomical regions of the MICCAI atlas were joined in order to attain at least five channels per analysed region. We formed eight regions joining channels from 20 regions (the entorhinal cortex had no electrodes): (i) superior and middle occipital gyri; (ii) inferior occipital gyrus and occipital pole; (iii) lingual gyrus and occipital-fusiform gyrus; (iv) postcentral gyrus and its medial segment; (v) gyrus rectus and anterior, medial, and posterior orbital gyri; (vi) superior frontal gyrus and frontal pole; (vii) temporal pole and planum tempolare; and (viii) fusiform and parahippocampal gyri. We analysed 38 cortical regions (median 40.5 channels per region, range 6–178 channels). Thus, the total number of analysed regions used in the multiple comparison correction was 42, the 38 cortical regions, plus the four lobes presented in the previous subsection.

Power spectra of all investigated cortical regions are provided in the Supplementary material. Brain regions such as the posterior insula, the anterior cingulate, and others did not show deviations from the no-peak set. In contrast, other brain regions demonstrated a specific signature: significant peaks present in more than 60% of the channels within a given region were found in the precentral gyrus (lateral segment: 64% of 123 channels at ~20–24 Hz; medial segment: 72% of 18 channels at ~24–31.5 Hz), the opercular part of the inferior frontal gyrus (72% of 39 channels at ~20–24 Hz), the cuneus (68% of 19 channels at ~8 Hz), and the hippocampus (72% of 36 channels at ~1 Hz) (Fig. 5).

Some cortical areas have more than one spectral peak within the same channel

From all analysed channels, 141 (7.9%) had more than one peak in the spectrum (comparing each channel to the no-peak set, without correcting for multiple comparisons). The percentage of channels with two or more peaks was significantly higher than the average of 7.9% in eight brain regions (cumulative binomial distribution with parameters theta = 0.079 and k = number of channels in the region, uncorrected). Most of these regions are sensory/motor regions: medial segment of the precentral gyrus (5/18 or 28% of channels), mid-cingulate region (8/40 or 20%), supplementary motor cortex (11/47 or 23%) and the cortex anterior to the supplementary motor cortex (3/16 or 19%), transverse temporal gyrus (3/14 or 21%), inferior occipital gyrus (4/20 or 20%), precentral gyrus (23/123 or 19%), and postcentral gyrus (11/65 or 17%).

In one-third of these channels (48/141) the second peak is at twice the frequency of the first (second harmonic), and in 8% (11 channels) there was a significant peak at the third harmonic. Half of the channels with second harmonics (24/48) correspond to the precentral gyrus, its medial segment, or the postcentral gyrus. Nine of the 11 channels with significant third harmonic belong to these regions.

The statistical test to determine if there are two significant peaks at different frequencies requires a multiple-comparison correction for a high number of 231 frequency pairs; therefore the results are not significant for the available number of channels.

Unexpected findings

In this section, we present some highlights of the findings for a few brain regions. For findings from all 38 brain regions, see the Supplementary material as well as the raw data, which are made available through our webpage (https://mni-open-ieegatlas.research.mcgill.ca).

The anterior insula cortex shows a beta peak

The insula cortex did not show a significant difference compared to the no-peak set. When subdividing the insula into an anterior and posterior portion, we found a peak in beta activity for the anterior insula in 34% of 71 channels (~20 Hz). There was no significant difference in the spectral power density between the posterior insula and the no-peak set (Supplementary material).

The middle cingulate gyrus shows a beta peak

The middle cingulate gyrus showed a beta peak (40% of 40 channels ~24 Hz, range: 19.75–24.25 Hz), but there was no difference of the power spectral density compared to the no-peak set for the anterior and posterior cingulate gyrus (Supplementary material).

Generation of alpha activity in occipital, parietal and temporal lobes

Alpha activity was present in a large portion, but not all regions of the occipital lobe (Fig. 6). The cuneus was the region with the highest number of channels showing a clear alpha peak (68% of 19 channels ~8 Hz, range: 7.75–9.75 Hz). This was even more expressed than in the calcarine cortex (58% of 12 channels ~9 Hz, not significantly different than the no-peak set, presumably because of the relatively low number of channels in the region). There was no significant alpha peak in the inferior occipital gyrus.

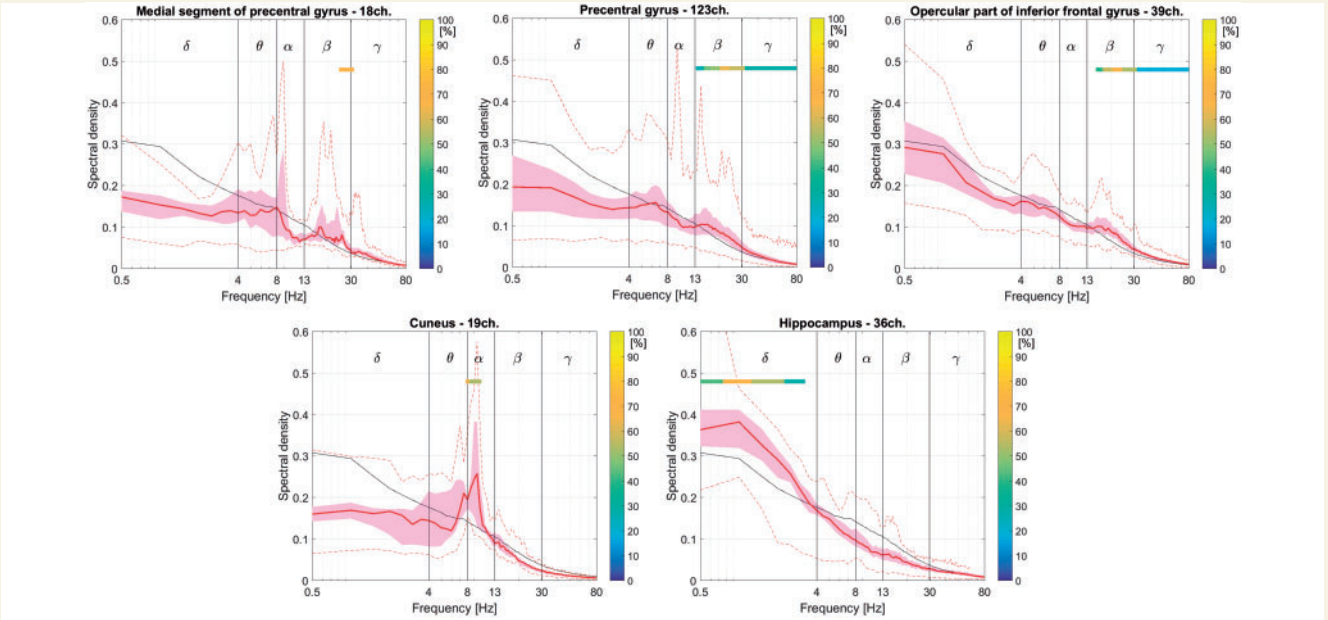

Figure 5 Spectral density plots of cortical regions showing a significant spectral density peak in >60% of investigated channels.

Apart from the occipital lobe, alpha activity was present, albeit in a lesser degree, in the superior parietal lobule (38% of 53 channels ~9 Hz, range: 8.25–9.25 Hz) and in some temporal regions, but at a lower frequency and at the limit of the traditional theta and alpha bands. These findings were significant for the superior temporal gyrus (35% of 79 channels ~8 Hz, range: 6.75–9.25 Hz) and the fusiform and parahippocampal gyri (49% of 45 channels ~8 Hz, range: 6.75–9.25 Hz) (Fig. 6). No significant peak in alpha activity was seen in the middle and inferior temporal gyrus, the temporal pole and planum temporale, the transverse temporal gyrus and the mesial temporal lobe structures, or in the angular gyrus, supramarginal gyrus, the pars opercularis, precuneus and posterior cingulate gyrus.

Some regions show significant peaks in delta activity during wakefulness

The most expressed peak in the delta range was found for the hippocampus (72% of 38 channels ~1 Hz, range: 0.5–3.25 Hz). Other regions with a delta peak were the inferior occipital gyrus and occipital pole (48% of 23 channels ~1.5 Hz, range: 1.25–3.25 Hz), the angular gyrus (38% of 53 channels ~1 Hz, range: 0.5–1.25 Hz), the medial frontal cortex (42% of 19 channels ~1 Hz, range: 0.5–1.25 Hz), the gyrus rectus/orbital cortex (42% of 45 channels ~1 Hz, range: 0.5–1.75 Hz), and the middle temporal gyrus (31% of 129 channels ~1 Hz, range: 0.5–1.75 Hz) (Fig. 7).

Analysis of the non-oscillatory component of the signal

We explored the scale-free brain activity by fitting a $1/f^{\beta}$ model to the high frequency end of the spectrum (10–40 Hz). We observed a median value of the β coefficient of 2.29 (range 0.68–4.26; mean 2.35; SD 0.52). We found different median β coefficients at a 5% significance level for the following regions: the β coefficient was higher (steeper decrease of the spectrum for increasing frequency) in the fusiform and parahippocampal gyri (45 channels, median $\beta = 2.84$, corrected $P = 0.0004$) and in the inferior occipital gyrus and occipital pole (23 channels, median $\beta = 2.78$, corrected $P = 0.024$), whereas it was lower in the middle frontal gyrus (178 channels, median $\beta = 2.11$, corrected $P = 0.001$). Figure 8A shows the distribution of the β coefficient in the different brain regions.

Regarding the nested-frequencies analysis, we found a low proportion of channels with significant phase-frequency coupling, likely because of the limited duration of the recordings. Figure 8B shows the proportion of channels with statistical significance at 5% without correcting for multiple comparisons (330 phase-amplitude bins), and Fig. 8C corrected for false discovery rate of 5%. In both cases the highest proportion is found between low delta (0.5 Hz) and low alpha band (8–10 Hz). But the proportion of channels in which this coupling was significant is low after correcting for multiple comparisons (28 channels, 1.5% of the 1785 available channels). We found no significant differences between regions.

Discussion

This is the first atlas of normal intracranial EEG of the adult human brain. Data from physiological channels of many patients with epilepsy were collected to overcome the limited sampling of the brain with intracranial electrodes and the unusual recording from presumably normal brain regions. Furthermore, to superimpose the

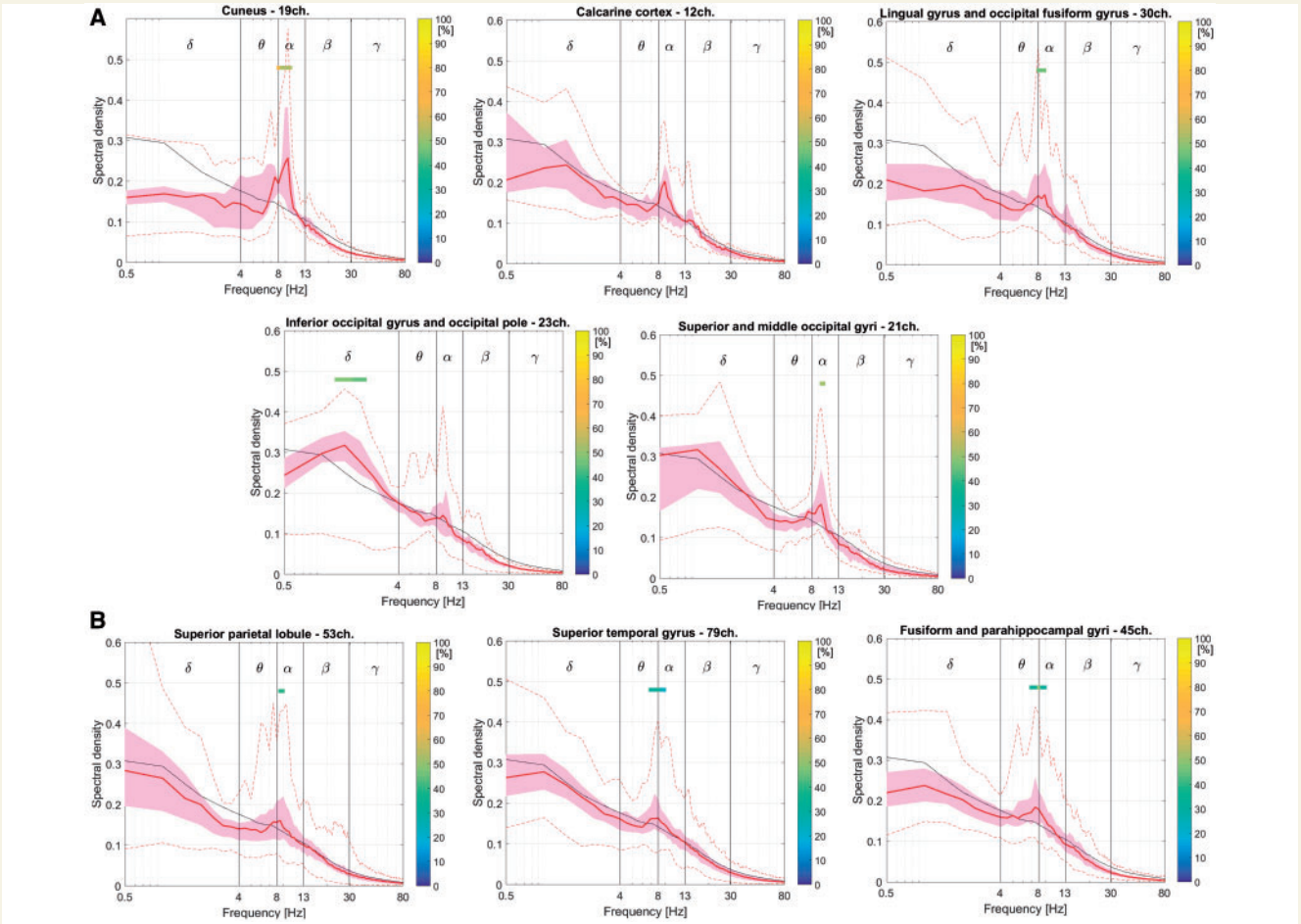

Figure 6 Presence of peaks in alpha activity across the brain. (**A**) Power spectral density plots of brain regions in the occipital lobe. (**B**) Power spectral density plots of brain regions outside the occipital lobe with significant alpha activity.

results from all subjects on one brain, intracranial electrode positions were standardized in a common 3D environment using a stereotactic template providing the exact coordinates of each recording contact. This atlas of normal brain activity will aid in the better differentiation between physiological and pathological brain activity for clinical work and research in humans. In this paper, results of the quantitative analysis obtained from a large population of human subjects are illustrated. This atlas will be an open resource available for consultation on the web developed under the LORIS framework (Das *et al.*, 2016).

Selection of channels from presumably normal brain regions

We are aware that selecting 'true' normal healthy cortex represents an inaccurate task, since we essentially analyse EEGs from the brains of epileptic patients. In most of these patients, however, some electrodes are placed in non-epileptogenic zones devoid of structural or physiological anomalies. These electrodes are necessary for comparison of cortical physiology and help to define the limits of the eventual surgical resection. Some presumably normal superficial neocortical regions are also recorded as a result of the need to reach a deep structure with a multi-contact electrode. Selecting the most normal brain regions in these patients is as close as we can ever get to a 'true' atlas of the normal brain. To ensure as much as possible the selection of channels with normal physiological EEG activity, we followed a strict protocol that involved the consensus of two epileptologists for selection of all the imaging and neurophysiological data for each subject (see 'Materials and methods' section). Even if a few channels from pathological regions might have slipped through our careful screening process, it is unlikely to have occurred for many, and the large number of channels in each region makes it likely that our average results are representative of the healthy brain.

Intracranial EEG data from different brain regions

This atlas extends our knowledge on cortical neurophysiology in humans by providing quantitative and accurate

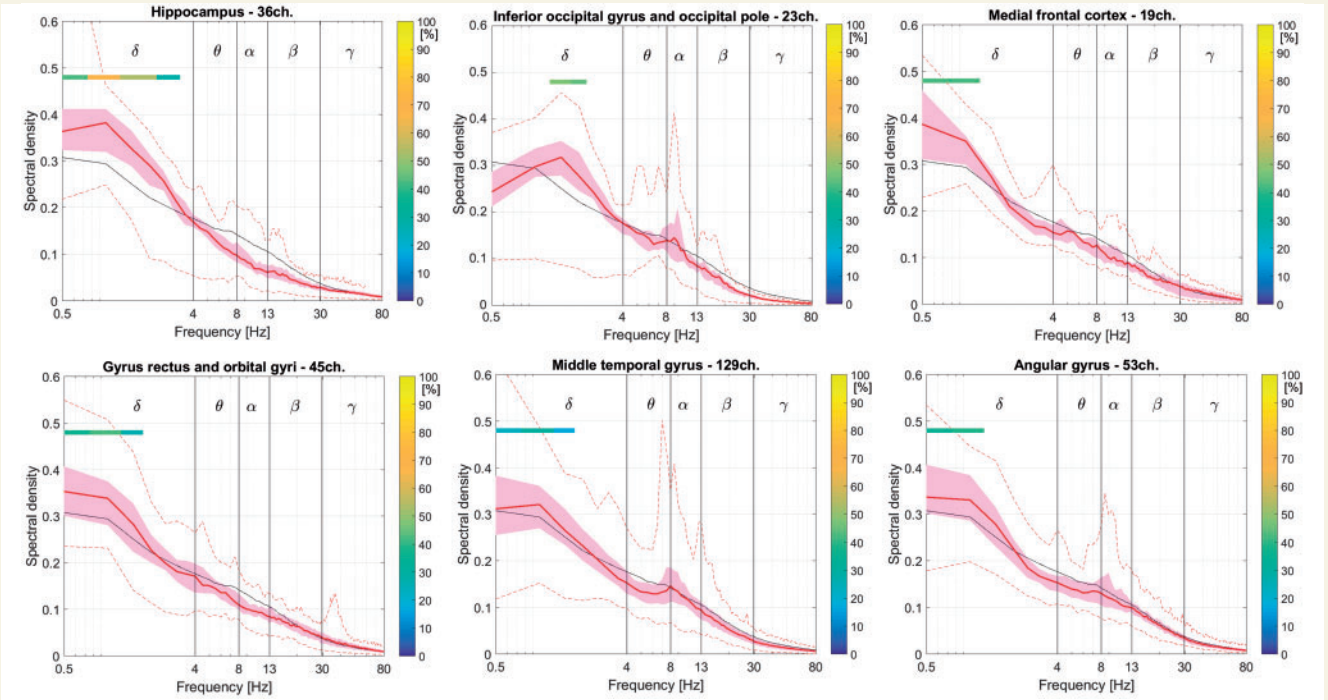

Figure 7 Power spectral density plots of brain regions with significant delta activity.

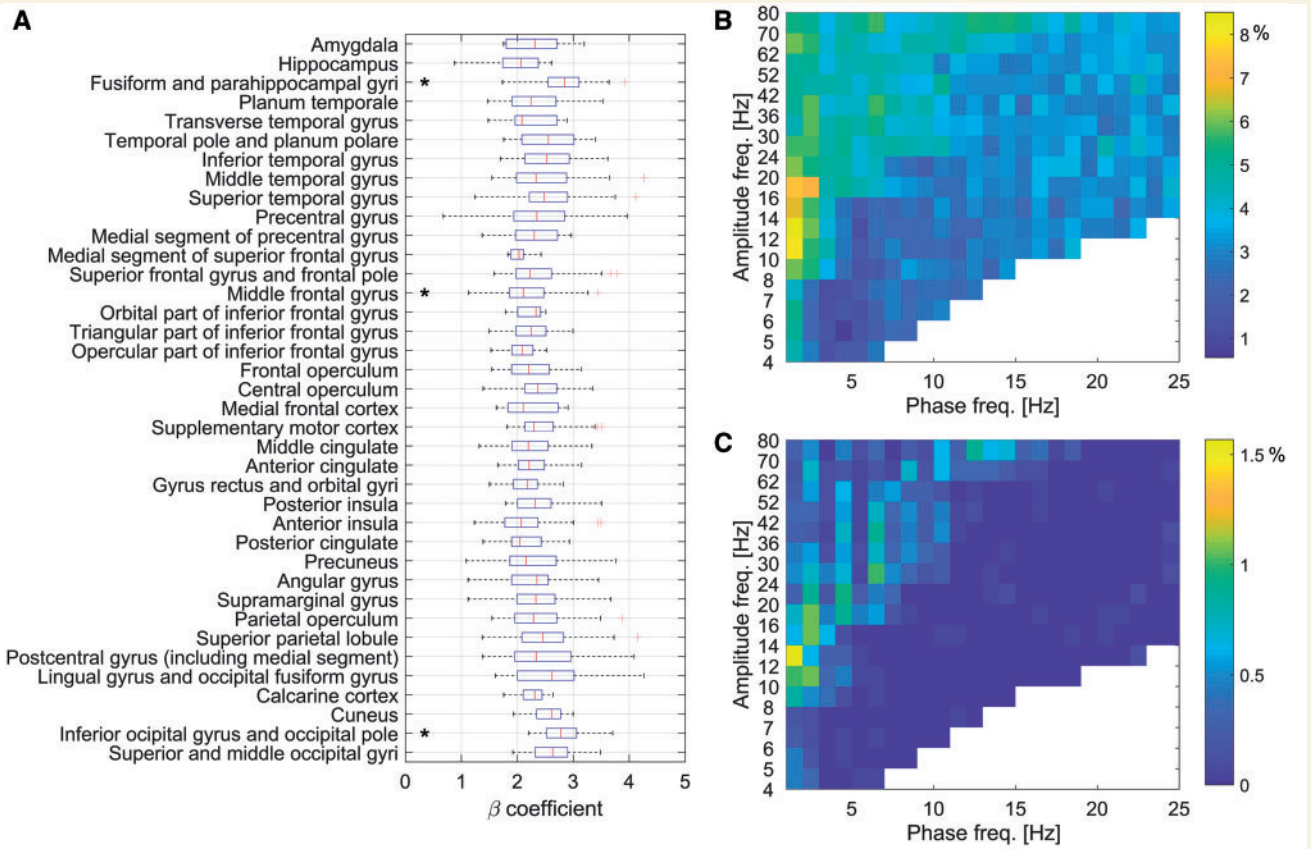

Figure 8 Analysis of the non-oscillatory component of the signal. (**A**) Distribution of the β coefficient of the 1/fβ model of the scale free component of the spectrum (10–40 Hz), i.e. the spectrum after removing peaks associated to oscillatory activity. The asterisks indicate regions with coefficient significantly different from the rest. (**B**) Percentage of channels showing statistically significant phase-amplitude coupling at different frequencies (uncorrected). (**C**) Percentage of channels showing statistically significant phase-amplitude coupling at different frequencies (corrected for false discovery rate of 5%).

EEG data for 38 different brain regions. In each region, an average of 2.7 channels per cm^3 of cortical grey matter was used for EEG recording. The best coverage was obtained in the areas most frequently explored during epilepsy surgery evaluation, the fronto-temporo-parietal regions. Less frequently explored areas such as the occipital cortex were, however, sufficiently covered. We were also able to identify channels with physiological activity in the mesiotemporal lobe structures, an area often explored, but usually showing epileptic activity.

Superimposition of all channels in a common stereotactic 3D environment

The lack of standardization in electrodes insertion and placement results in problems performing inter individual comparisons of EEG patterns and, hence, obtaining normative electrophysiological data. To overcome this problem, we used a common 3D environment (IBIS) for semi-automatic co-registration and superimposition of the results from all electrodes from all subjects on one brain template (Mazziotta *et al.*, 2001). To avoid potential bias by a human scorer in the assignment of electrode contacts to anatomical regions, anatomical structures were automatically segmented using an atlas created with an unbiased method (Fonov *et al.*, 2011). This atlas provided detailed volumetric tissue classification of cortical and deep structures (e.g. hippocampus, amygdala). Full brain volume coverage with 66 labels per hemisphere allowed proper assignment of electrode contacts to the anatomical region from which they most likely record.

Comparison of stereo-EEG electrodes and cortical grids or strips

Compared to scalp EEG, intracranial recordings are not standardized and may show interindividual variations. Stereo-EEG electrodes are in direct contact with the neuronal generators, with a spatial organization that is highly variable and does not follow a standardized electrode positioning like for the 10-20 or 10-10 International EEG System (Jasper, 1958; Nuwer *et al.*, 1998). In contrast, grids/strips have the same distance to the cortical surface and are therefore in the same position with respect to the cellular organization of the cortex.

Our study demonstrated that there was no difference in the spectral power distribution between EEG recordings performed with stereo-EEG and cortical grids/strips. The absolute amplitude was two times higher using cortical grids/strips as compared to stereo-EEG. This might be because of the location and orientation of the electrodes with respect to the cortical sources. In case of grids/strips the electrode contacts are always localized atop of the cortex, whereas there are different orientations in stereo-EEG regarding the cellular organization of the cortex.

Region-specific EEG signatures as assessed with spectral power analysis

After discussing methodological issues we now discuss the main findings. The present work aimed at identifying rhythms characteristic for the different brain regions. To do so we calculated spectral density plots for the different regions investigated. Significances in spectral frequencies were calculated by performing a comparison with a group of automatically selected channels exhibiting no spectral peaks ('no-peak' channels). This is a first step in analysing the available data and identifying region-specific characteristics to improve our knowledge on the cortical structural-functional interrelations. Indeed, different methods could have been used. The availability of the present data will allow others to apply different methods and provide further characterization of the human normal iEEG.

Distribution of rhythmic activity across different brain regions

Current evidence suggests that rhythms are important for the communication between different brain regions (Steriade, 2006; Buzsaki and Schomburg, 2015). To study such rhythms and interactions systematically, it is important to have knowledge of the basic rhythms of each brain region at rest, which is provided by the current atlas. A recent study using MEG in 22 healthy subjects investigated whether rhythmic brain activity is characteristic for different cortical areas. The authors found that individual human brain areas can be identified from their characteristic spectral activation patterns. Moreover, clustering of brain areas according to similarity of spectral profiles reveals known brain networks (Keitel and Gross, 2016). Data of the present atlas could be used to validate these results, and extend them because of the difficulty of MEG to assess deep sources. Another recent study examined brain rhythms of the sensorimotor region in 20 healthy subjects using 64-channel scalp EEG. This study is interesting, although limited to the central region only, as it is a first step towards the identification of cortical areas based on neuronal dynamics rather than on cytoarchitectural features (Cottone *et al.*, 2017). An extension of this work could be to apply this methodology to the intracranial atlas.

Focal generation of alpha activity

Early work in the canine model demonstrated that the alpha rhythm is generated in the cerebral cortex (Lopes da Silva and Storm Van Leeuwen, 1979). These data obtained by invasive EEG are complemented by more recent non-invasive studies using source analysis showing that the alpha rhythm is due to more than one generator in the posterior cortex. Moreover, a thalamic modulating influence has been suggested (Tyvaert *et al.*, 2008; Chang *et al.*, 2011). Findings from electrocorticography and intracerebral depth EEG studies described alpha activity in the

occipital lobe, the parietal lobe just posterior to the postcentral gyrus, and in the posterior temporal neocortex (Frauscher and Dubeau, 2018). Our present work confirmed in part these findings. Interestingly and in contrast to what we initially suspected, a clear peak in alpha activity was not found in all occipital lobe structures; it was most prominent in the mesio-occipital lobe and in particular in the cuneus. Alpha activity was further seen in the superior parietal lobe, as well as the temporal lobe. In the latter, alpha activity was of a lower frequency compared to the occipital lobe. Moreover, there was a peak in alpha activity in the postcentral gyrus. We did not find alpha activity in the frontal lobe, as previously described (Jasper and Penfield, 1949).

Peak in beta activity in motor function-related cortical areas

In the motor system, oscillations in the beta frequency band have been suggested to play a role in sensorimotor integration (Baker, 2007). Of note, a vast majority of motor function-related eloquent neocortical areas such as the precentral gyrus, the supplementary motor cortex, the mid-cingulate, the anterior insula, the pars triangularis of the inferior frontal gyrus, and the operculum showed a significant peak in the beta frequency band during resting state. This beta peak was most evident in the precentral gyrus, as suggested by previous work during acute electrocorticography (Jasper and Penfield, 1949). In line with our findings, studies examining the execution of voluntary movements showed, in primary sensorimotor areas, a desynchronization of beta activity with the motor response, followed by the appearance of an event-related synchronization in the gamma range between 40 and 60 Hz, and reappearance of beta activity (Sem-Jacobsen *et al.*, 1956; Pfurtscheller and Lopes da Silva, 1999; Szurhaj and Derambure, 2006).

Presence of frequency peaks in the different bands depends on the brain region

A new finding of this study is that there is more than one peak in certain brain regions, even within the same EEG channel. One example is the precentral gyrus. All channels in this cortical region showed more than one peak in the delta, theta and high beta range. Previous work using acute electrocorticography showed a fast beta rhythm of 25 Hz similar to that in our study in the precentral area (Jasper and Penfield, 1949), but did not refer to underlying slower frequency bands. We further confirmed peaks in alpha and beta activity in the postcentral gyrus. This finding is in line with the notion that there is less beta activity in the postcentral gyrus when performing a direct comparison to the precentral gyrus (Jasper and Penfield, 1949).

It is noteworthy that there are certain brain regions, particularly in the temporal lobe or in deep structures such as the anterior and posterior cingulate gyrus as well as the posterior insula, which did not show any difference (statistically significant or perceptible visually) with the set of channels with no identifiable spectral peaks. For other regions, such as the calcarine cortex, there was a clear peak in certain frequency bands, which, however, was not significant, most likely because of the relatively small number of investigated channels.

Presence of focal cortical peaks in the delta band in the awake brain

Slower frequencies in the theta delta range were found in frontobasal, as well as frontomesial and temporomesial structures. Delta activity in the ventral medial frontal brain portions was already suggested by Sem-Jacobsen *et al.* (1955) and for the orbitofrontal cortex by Nishida *et al.* (2004). Slow wave activity in the hippocampus, consisting of irregular slow waves in the delta and theta frequency range was also already reported in the past (Jasper and Penfield, 1949; Brazier, 1968). Interestingly, previous studies showed that the EEG activity in the hippocampus is task-dependent (Bódizs *et al.*, 2001; Cantero *et al.*, 2003; Clemens *et al.*, 2009; Lega *et al.*, 2012; Moroni *et al.*, 2012; Watrous *et al.*, 2013; Billeke *et al.*, 2017). Findings of the present study are in line with the described 'large irregular activity' characterized by hippocampal sharp waves occurring during immobility. In this context, it is noteworthy to stress that in humans, this slow wave activity is in the delta range; in animals it was shown to be in the theta range (Bódizs *et al.*, 2001; Clemens *et al.*, 2009; Watrous *et al.*, 2013).

Analysis of the non-oscillatory component of the signal

The classical frequency bands in EEG are described based on the various oscillatory rhythms that appear in the EEG. Apart from this oscillatory component, the EEG has a significant, if not major, component of non-oscillatory or scale free activity. We analysed both components and observed differences in the non-oscillatory EEG signal in different brain regions, with higher values in the fusiform and parahippocampal gyri, as well as the inferior occipital gyrus and occipital pole. All these regions are involved in visual processing. Interestingly, this is in keeping with a study analysing scale free activity with functional MRI that showed increased values for the visual cortex (He *et al.*, 2010). We further analysed our data for nested frequencies. We found the strongest phase amplitude coupling between the phase of very low frequency activity at 0.5 Hz and the low alpha band amplitude. The low proportion of channels with significant coupling compared e.g. to He *et al.* (2010), might be explained by the short length of the recordings in the awake/eyes closed condition.

Conclusion and future prospects

This is the first atlas of normal intracranial EEG activity in a common stereotactic space that allows the accumulation of small amounts of data from each of a large group of subjects, to obtain an atlas covering well most cortical regions. It will aid the neurophysiologist to understand the EEG frequency distributions across the different cortical regions of the human brain better. This atlas provides a normative baseline against which clinical EEGs and experimental results can be compared. It will be an open resource available for augmentation and consultation on the web (https://mni-open-ieegatlas.research.mcgill.ca). We are currently preparing an atlas on sleep, as sleep data are available from most of the subjects and we will be able to compare wake and sleep across the different investigated regions. Also, we still have some regions that are not fully covered, but we intend to allow the atlas to grow by inclusion of data from the original centres as well as from other qualified centres, and to continue the current project in a prospective way. This will also allow to collect longer segments of controlled awake/eyes closed condition for different types of analysis, such as that of nested frequencies.

Acknowledgements

The authors wish to express their gratitude to Louis Collins, PhD, Vladimir Fonov, PhD, as well as Alan Evans, PhD and the LORIS team from the McConnell Brain Imaging Centre of McGill University, as well as the staff and technicians at the EEG Department at the Montreal Neurological Institute and Hospital, Lorraine Allard, Nicole Drouin, Chantal Lessard and Linda Ménard, the staff and technicians at the Neurophysiopathology Laboratory of Grenoble-Alpes University Hospital, Dr. Anne-Sophie Job-Chapron, Patricia Boschetti, and Marie-Pierre Noto, and the staff and technicians at the Centre Hospitalier de l'Université de Montréal.

Funding

This work was supported by the Savoy Epilepsy Foundation (project grant to B.F. and post-doctoral fellowship to R.Z.), the Botterell Powell's Foundation (grant to B.F.), and the Canadian Institute of Health Research (grant FDN-143208 to J.G.).

Conflicts of interest

The authors have no potential conflict of interest with the present study. Outside of the submitted work, B.F. received speaker/advisory board fees sponsored by UCB. J.G. and N.v.E. have received fees for consultancy from Precisis Inc. P.K. received speaker/advisory board fees from UCB and Eisai. D.K.N., D.H., F.D., J.H., L.M., A.O., and R.Z. have nothing to declare.

Supplementary material

Supplementary material is available at *Brain* online.

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Annex 3: Dolezalova I, Brazdil M, Hermanova M, Horakova I, Rektor I, Kuba R. Intracranial seizure onset patterns in unilateral temporal lobe epilepsy and their relationship to other variables. Clinical Neurophysiology. 2013;124(6):1079-1088.

Clinical Neurophysiology 124 (2013) 1079–1088

Contents lists available at SciVerse ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Intracranial EEG seizure onset patterns in unilateral temporal lobe epilepsy and their relationship to other variables

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ARTICLE INFO

Article history:
Accepted 28 December 2012
Available online 13 February 2013

Keywords:
Temporal lobe epilepsy
Invasive EEG
Outcome
Histopathology
Localization
Frequency
Predictive factors

HIGHLIGHTS

- Very early seizure onset frequencies in invasive EEG in patient with temporal lobe epilepsy could be predictive factor for their outcome.
- Higher frequencies (⩾8 Hz) could indicate better surgical outcome.
- Slower frequencies (<8 Hz) could imply worse surgical outcome.

ABSTRACT

Objective: We performed a retrospective study to determine the different types of seizure onset patterns (SOP) in invasive EEG (IEEG) in patients with temporal lobe epilepsy (TLE).
Methods: We analyzed a group of 51 patients (158 seizures) with TLE who underwent IEEG. We analyzed the dominant frequency during the first 3 s after the onset of ictal activity. The cut-off value for distinguishing between fast and slow frequencies was 8 Hz. We defined three types of SOPs: (1) fast ictal activity (FIA) – frequency ⩾8 Hz; (2) slow ictal activity (SIA) – frequency <8 Hz; and (3) attenuation of background activity (AT) – no clear-cut rhythmic activity during the first 3 s associated with changes of IEEG signal (increase of frequency, decrease of amplitude). We tried to find the relationship between different SOP types and surgery outcome, histopathological findings, and SOZ localization.
Results: The most frequent SOP was FIA, which was present in 67% of patients. More patients with FIA were classified postoperatively as Engel I than those with SIA and AT (85% vs. 31% vs. 0) ($P < 0.001$). There were no statistically significant differences in the type of SOP, in the histopathological findings, or in the SOZ localization.
Conclusion: In patients with refractory TLE, seizure onset frequencies ⩾8 Hz during the first 3 s of ictal activity are associated with a better surgical outcome than frequencies <8 Hz.
Significance: Our study suggests that very early seizure onset frequencies in IEEG in patients with TLE could be the independent predictive factor for their outcome, regardless of the localization and etiology.

1. Introduction

Temporal lobe epilepsy (TLE) is the most common form of drug resistant partial epilepsy (Williamson et al., 1998). Epilepsy surgery is a well-established and evidence-based method for treatment in TLE patients (Wiebe et al., 2001). In the context of epilepsy surgery, the precise identification of the epileptogenic zone, which is defined as the zone responsible for seizure generation and which has to be removed completely for seizure freedom, is crucial (Bancaud et al., 1965; Lüders and Awad, 1992; Rosenow and Lüders, 2001). There is currently no diagnostic modality that can be used to measure the entire epileptogenic zone directly. We can deduce the extent of the epileptogenic zone only indirectly from the seizure onset zone (SOZ) (Rosenow and Lüders, 2001). In cases where the SOZ cannot be properly identified on the basis of non-invasive investigations, invasive electroencephalography (IEEG) monitoring is a well-established method for its localization (Wyler et al., 1984, 1993; Devinsky et al., 1989; Spencer, 1989; Sperling and O'Connor, 1989; Spencer et al., 1990, 1993; So, 1992, 1995; Arroyo et al., 1993; Spencer and Lamoureux, 1996).

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1388-2457/$36.00
http://dx.doi.org/10.1016/j.clinph.2012.12.046

The major limitation of IEEG is the recording of cerebral activity from an extremely confined region; the SOZ can be missed or falsely localized to the regions with propagated electrographic seizure activity (Spencer et al., 1982, 1993; Gloor, 1984; So, 1992, 1995; Arroyo et al., 1993; Spencer and Lamoureux, 1996).

It has been suggested that the different morphologies of intracranial EEG seizure onsets have different degrees of localizing value (Lieb et al., 1981; Engel et al., 1989; Engel, 1990; Faught et al., 1992; Weinand et al., 1992; Spencer, 1994; Park et al., 1996). Published studies with subdural (Weinand et al., 1992) and epidural (Faught et al., 1992) electrodes in patients with TLE showed that fast activity at seizure onset can be associated with seizure freedom after surgery. In some studies, slower ictal onset frequencies, mainly from the theta range, in intracranial electrodes in patients with TLE can suggest a "propagated" electrographic pattern (Schiller et al., 1998). Engel et al. (1989) separated patients with TLE into two groups according to their ictal onset patterns: hypersynchronous patterns (HYP) and low-voltage fast patterns (LVF), which are described in 70–80% of patients (Engel, 1990; Velasco et al., 2000; Ogren et al., 2009). Many investigators focus on the qualities of these two patterns, mainly in terms of the predominant localization and histopathological findings (Lieb et al., 1981; Townsend and Engel, 1991; Spanedda et al., 1997; Spencer et al., 1992a,b; Velasco et al., 2000; Schiller et al., 1998; Ogren et al., 2009). Patients who cannot be classified according to these criteria are not included in most studies of seizure classification (Bragin et al., 2005), resulting in the loss of important information.

In the present study, patients with medically refractory TLE were categorized into three groups according to the seizure onset frequencies recorded in IEEG. These three groups were then correlated according to surgical outcomes, SOZ localizations, and histopathological findings. We hypothesized that this approach would reveal variations between frequency groups and patient characteristics.

2. Methods

2.1. Patient selection

In this retrospective study, we included all patients with refractory TLE who underwent epilepsy surgery at the Brno Epilepsy Center of Masaryk University Hospital between 1996 and 2011 and who had undergone IEEG prior to the surgery. Other inclusion criteria were: (1) IEEG showing that SOZ is restricted to unilateral temporal lobe structures (we excluded patients with bitemporal independent SOZs and patients with contemporary involvement of temporal and extratemporal lobe structures); (2) surgery performed according to non-invasive data and IEEG results; and (3) at least 1 year of follow-up after the surgery. We included a total of 51 patients who fulfilled these criteria. All patients gave their informed consent. The study was approved by the ethics committee of St. Anne's University Hospital.

2.2. Presurgical evaluation

All 51 patients underwent a comprehensive evaluation, including detailed history and neurological examination, neuropsychological testing, magnetic resonance imaging (MRI), and both scalp and invasive video-EEG monitoring. Fluorodeoxyglucose-positron emission tomography (FDG-PET) and/or interictal single photon emission tomography (SPECT) was performed in all patients; other functional neuroimaging techniques such as ictal SPECT and subtraction ictal SPECT co-registered to MRI (SISCOM) were performed only in patients with incongruent preoperative data. In total, 37 patients had MRI abnormalities prior to surgery. The remaining 14 patients showed no clear MRI abnormalities.

2.3. Invasive EEG procedure

All patients underwent the IEEG procedure. Of the 51 patients, 47 were investigated with chronically stereotactically implanted intracerebral electrodes. The number of electrodes per patient ranged from 3 to 14 (with an average of 7.9 ± 2.2). In 4 patients, we used a combination of 1 or 2 stereotactically implanted intracerebral electrodes and subdural strip electrodes. In three cases 8-contact strips were used, and in 1 case a combination of 6-contact and 8-contact strips was used. In 20 out of 51 patients (40%), the exploration was limited to temporal lobe structures; in the other 31 patients (60%), extratemporal structures were explored as well.

The anatomical targeting of intracerebral electrodes and the position of subdural strips were established in each patient according to available non-invasive information and hypotheses about the localization of SOZ. Intracerebral 5-, 10-, and 15-contact platinum semiflexible Microdeep electrodes DIXI or ALCIS (with an electrode diameter of 0.8 mm, a contact length of 2 mm, and a 1.5 mm distance between contacts) and 6- and 8-contact platinum subdural strip electrodes (Radionics) were used. The invasive video-EEG recording was performed with the 64-channel Brain Quick system (Micromed), and the 128-channel Alien Deymed system was used for intracranial video-EEG recording. Monopolar recordings (with a reference electrode on the processus mastoideus) and special bipolar montages were used to evaluate the EEG activity. EEG was amplified with a bandwidth of 0.4–100 Hz at a sampling rate of 128 Hz.

2.4. Invasive EEG analysis

The character and localization of seizure onset (SO) were analyzed independently by two of the authors (ID & RK) and disagreement was resolved by consensus after review.

SO was assessed visually and defined as a sustained rhythmic change in the IEEG accompanied by subsequent clinically typical seizure activity, not explained by level of arousal and clearly distinguished from background IEEG and interictal activity (Spencer et al., 1992b).

We examined only seizures with clinical accompaniment, because the significance of pure electrographic seizures is not clearly determined (Sperling and O'Connor, 1990).

We divided the SOs according to their localization, as (1) mesial (amygdala, hippocampus, parahippocampal gyrus), (2) temporopolar, and (3) laterobasal (laterobasal cortex dorsally from temporal pole). The temporal pole delineation defined by Chabardès et al. (2002) was applied. The posterior border of the temporal pole region was taken as an oblique line joining the rostral ends of the superior and inferior temporal sulci projected onto another line passing through the anterior edge of the temporofrontal transitional fold. On the basal side, the border passed through the rostral end of the inferior temporal sulcus and terminated at the rhinal sulcus in the mesial part of the hemisphere (Chabardès et al., 2002).

We analyzed the frequency of SO during the first 3 s of ictal activity as defined above. The dominant frequency of each SO was determined based on spectral analysis, using the fast Fourier transform algorithm, and was defined as a frequency with its maximal peak in the given spectrum. The dominant frequency was measured in the contact where the ictal activity first appeared. If the simultaneous involvement of two or more contacts was present, only the highest dominant frequency was used for analysis.

We conducted the frequency analysis according to the following principles:

- Some types of initial EEG changes, i.e., brief bursts of spikes and attenuation of the background activity lasting less than 3 s, were not considered part of seizure onset (Lee et al., 2000). If they were the initial EEG changes, we used the frequency of subsequent ictal activity.

- If there was a rhythmic pattern in some electrodes and attenuation of background activity in others, we classified this SO according to the frequency of the rhythmic activity, following a similar principle used by Lee et al. (2000).
- If the first change was an attenuation lasting more than 3 s and no rhythmic activity was present simultaneously, we defined it as a unique pattern.

The patients were divided into two groups according to the dominant SO frequency. The cut-off value to distinguish between fast and slow frequencies was 8 Hz, which was established as the lower borderline of the alpha frequency range. When 2 or 3 SOPs were present, the predominant pattern was used for the analysis; Lee et al. applied the same concept (Lee et al., 2000). This predominant pattern was defined as the most common pattern (more than half of all seizures) in an individual. If we were not able to determine the predominant pattern in a patient, this patient was excluded from further analysis.

Based on these criteria, we defined three types of seizure onset patterns (SOP):

Fast ictal activity (FIA) – frequency ⩾than 8 Hz (Fig. 1); slow ictal activity (SIA) – frequency <than 8 Hz (Fig. 2); attenuation of background activity (AT) – changes in the IEEG signal (decrease of amplitude, increase of frequency) preceding the development of a visible clear-cut rhythm by more than 3 s (Fig. 3).

Subsequently, the average frequency for each patient pattern except AT was counted; it was defined as the arithmetical average of each pattern's dominant frequencies. If the patients were categorized on the basis of a predominant pattern, only the dominant frequencies belonging to this predominant pattern were taken into account.

FIA and SIA were further subdivided according to average SO frequency:

(1) FIA was subdivided into 2 bands with a cut-off value of 15 Hz, i.e. frequencies between 8 and 15 Hz (FIA = 8–15 Hz) and frequencies higher than 15 Hz (FIA > 15 Hz).
(2) Similarly, SIA was subdivided into 2 bands with a cut-off value of 2 Hz, i.e. frequencies ⩽2 Hz (SIA ⩽ 2 Hz) and frequencies >2 Hz (SIA > 2 Hz). This separation was based on the works of Engel et al. (1989), who designated ictal onset activity of frequencies ⩽2 Hz as a HYP pattern.

2.5. Surgical procedure

The extent of the resection was based on the results of a presurgical evaluation including non-invasive and invasive data. Engel's

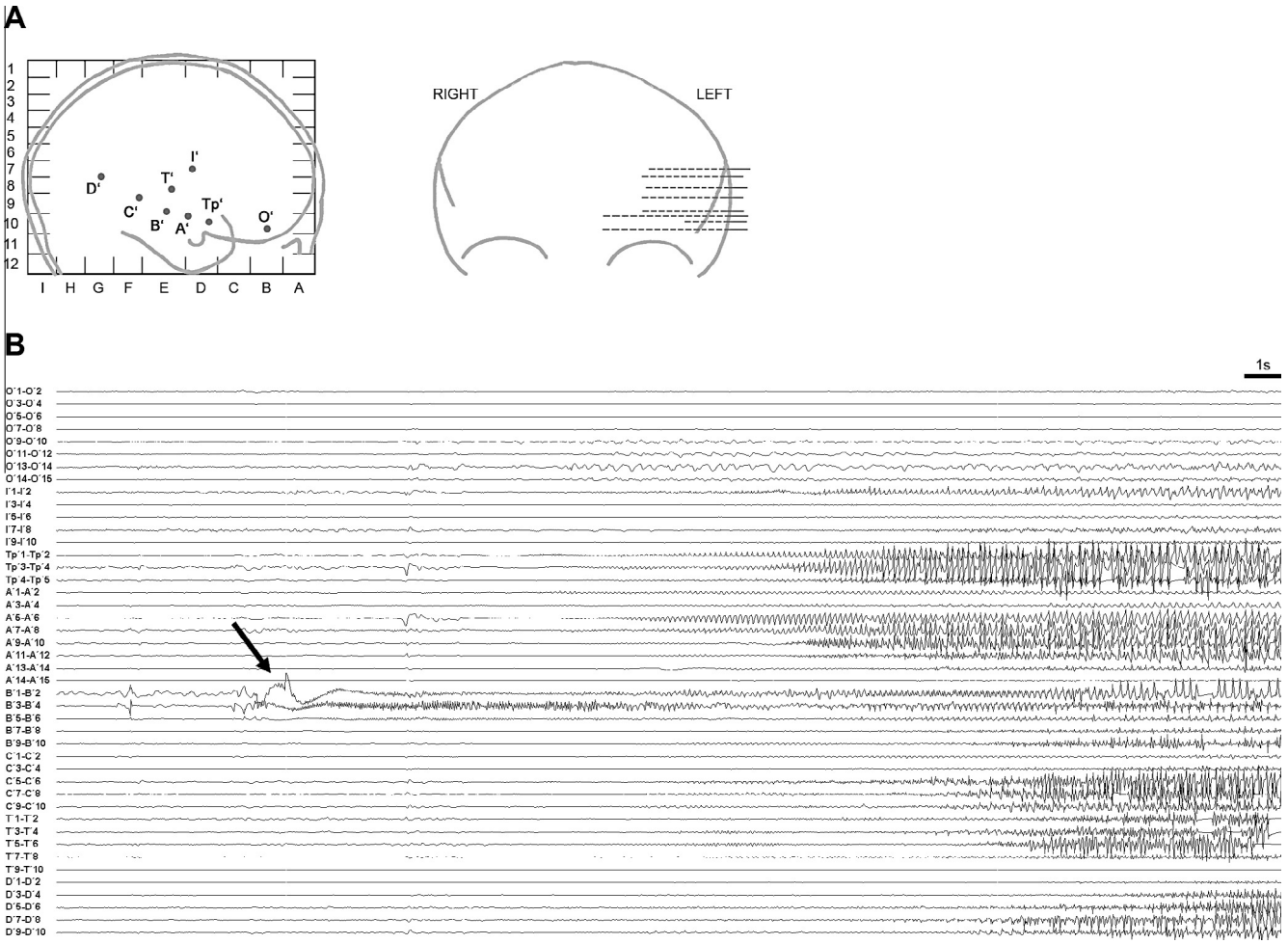

Fig. 1. Fast ictal activity (FIA). (A) Localization of intracerebral electrodes: electrodes on the left side: A′ – mesial, amygdala, lateral middle temporal gyrus; B′ – mesial anterior hippocampus, lateral middle temporal gyrus; C′ – mesial posterior hippocampus, lateral middle temporal gyrus; D′ – middle temporal gyrus (posterior part); T′ – superior temporal gyrus; Tp′ – temporal pole; I′ – frontal operculum; O′ – orbitofrontal cortex. (B) Ictal findings: the arrow indicates the development of FIA in B′ 1–4 (hippocampus on the left side).

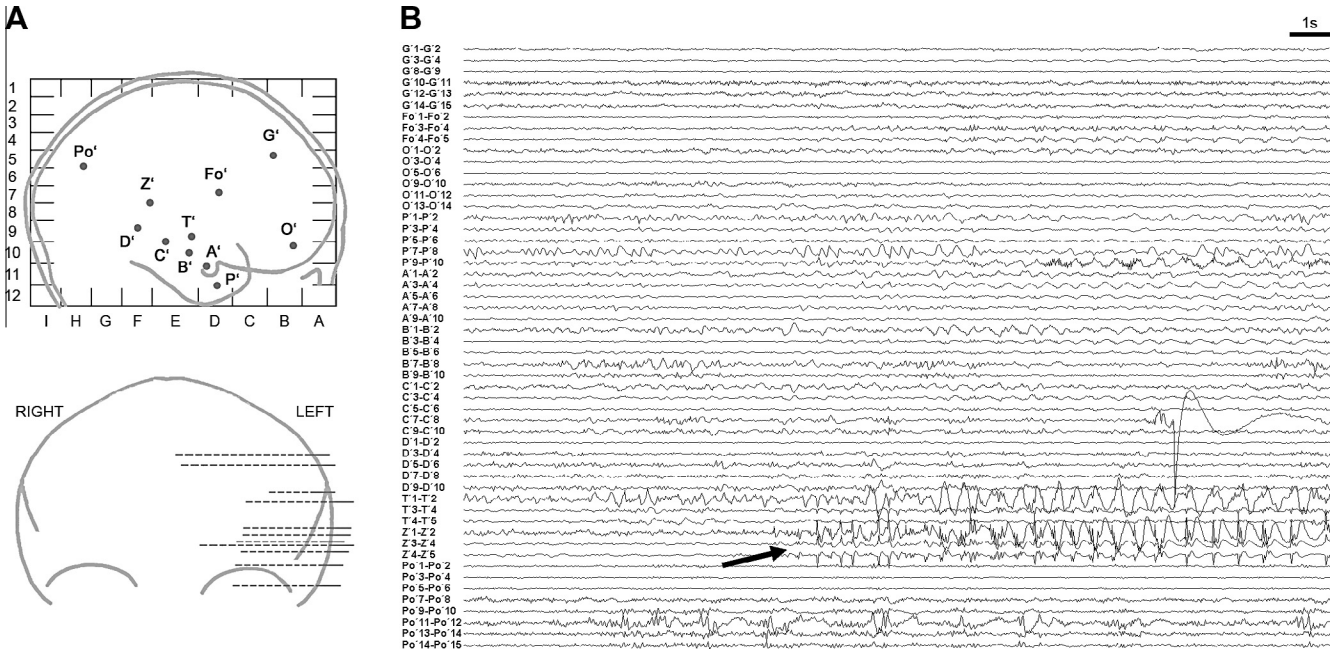

Fig. 2. Slow ictal activity (SIA). (A) Localization of intracerebral electrodes: electrodes on the left side: A′ – mesial amygdala, lateral middle temporal gyrus; B′ – mesial anterior hippocampus, lateral middle temporal gyrus; C′ – mesial posterior hippocampus, lateral middle temporal gyrus; D′ – middle temporal gyrus; P′ – temporal pole, T′ – superior temporal gyrus (posterior part); Z′ – superior temporal gyrus (anterior part); Po′ – precuneus; Fo′ – frontal operculum; O′ – orbitofrontal cortex. (B) Ictal findings: the arrow indicates the development of SIA in Z′ 1–4 (left superior temporal gyrus).

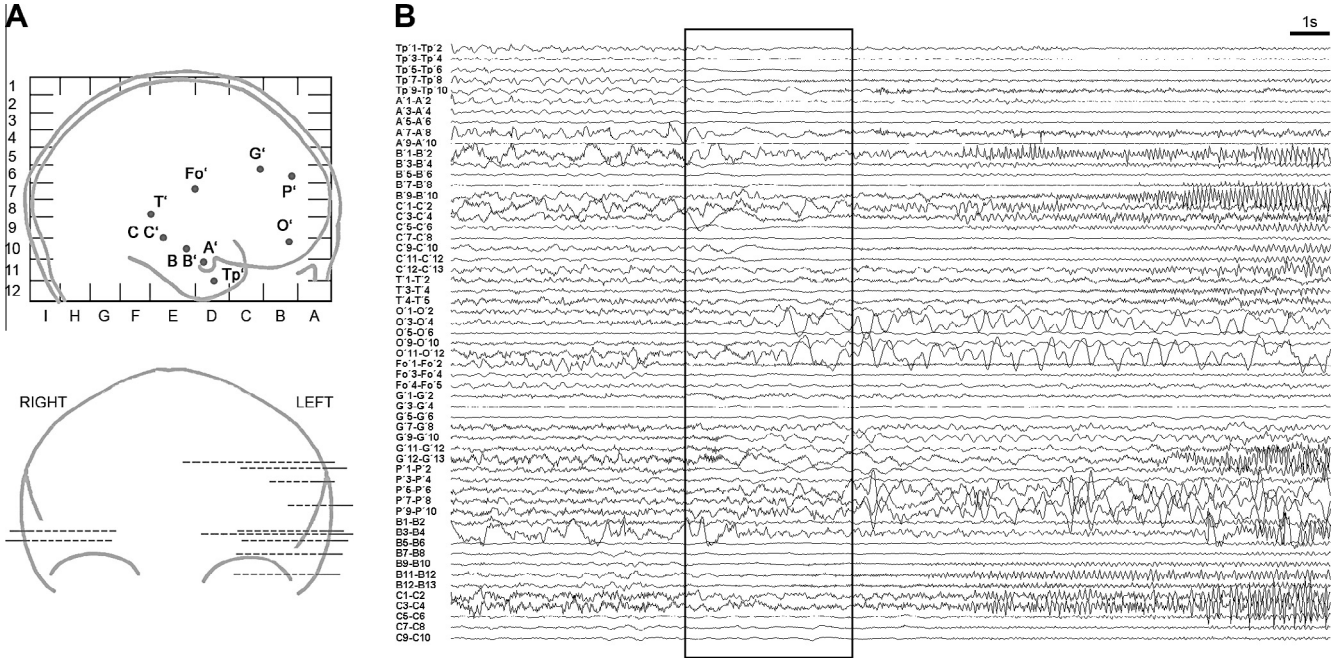

Fig. 3. Attenuation of background activity (AT). (A) Localization of intracerebral electrodes: electrodes on the left side: A′ – mesial amygdala, lateral middle temporal gyrus; B′ – mesial anterior hippocampus, lateral middle temporal gyrus; C′ – mesial posterior hippocampus, lateral middle temporal gyrus; T′ – superior temporal gyrus; Tp′ – temporal pole; O′ – orbitofrontal cortex; G′ – mesial anterior cingulate gyrus, lateral middle frontal gyrus; P′ – mesial medial frontal gyrus, lateral superior frontal gyrus; Fo′ – frontal operculum. Electrodes on the right side: B – mesial anterior hippocampus, lateral middle temporal gyrus; C – mesial posterior hippocampus, lateral middle temporal gyrus. (B) Ictal findings: AT appears initially in both left-sided and in right-sided electrodes (frame); this is followed, in approximately 5 s, by rhythmic ictal activity.

classification (Engel et al., 1987) was used to evaluate surgical effectiveness.

2.6. Neuropathological examination

Evaluable formalin-fixed paraffin-embedded tissues of temporal lobe resection specimens were available from all patients. The paraffin-embedded tissue specimens, slides, and histopathology reports were retrieved from the files of the First Department of Pathological Anatomy of St. Anne's University Hospital and independently re-evaluated by two histopathologists exprerienced in the evaluation of specimens obtained from epilepsy surgery patients (MH & IH), and discrepancies were resolved by consensus. All examined resected tissues were identically treated, fixed in a

10% neutral buffered formalin, grossly inspected, measured, and cut so as to obtain representative tissue slices perpendicular to the cortical surface. Representative tissue slices were routinely processed and paraffin embedded. Five micrometers thick tissue sections were stained by hematoxylin and eosin, evaluated under light microscope, and reported. NeuN immunohistochemistry (using mouse monoclonal anti-NeuN antibody, dilution 1:100, clone A-60, Millipore), was performed on preselected tissue sections if there was an inconclusive picture in hematoxylin and eosin.

Focal cortical dysplasias were classified according the classification system reported by Blümcke et al. (2011).

2.7. Statistical analysis

The Kruskal–Wallis test was used to test possible relationships between individual SOPs and patient demographic data, i.e. age at epilepsy onset, epilepsy duration, and age at time of surgery. The Wilcoxon–Mann–Whitney test was used to compare average frequencies between groups of patients with different Engel outcomes. The chi-square test was used to analyze the relationship between individual SOPs and surgical outcome, SOZ localization, and histopathological findings. The chi-square test was also used to analyze the relationship between surgical outcome and SOZ localization and histopathological findings. *P*-value <0.05 was considered to be statistically significant.

3. Results

3.1. Demographic data

The study included 51 patients: 20 females and 31 males. Patient age at the time of surgery ranged from 13 to 54 years (with an average of 31.5 ± 6.6 years). The age at epilepsy onset ranged from 0 to 42 years (with an average of 13.4 ± 7.4 years), and epilepsy duration ranged from 4 to 36 years (with an average of 18.3 ± 7.9 years). All data concerning the whole series of our patients are summarized in Table 1.

3.2. Surgery and outcome

Surgery was performed on the right side in 26 out of 51 patients (51%) and on the left side in 25 (49%). Standard anteromesial temporal lobe resection (AMTR) was done in 36 patients (70%), tailored lesionectomy in 12 patients (24%), AMTR plus tailored topectomy of the lateral temporal cortex in 2 patients (4%), and temporal pole resection sparing the hippocampus in 1 patient (2%).

Using Engel's classification, 33 (65%) patients were classified as Engel I, 5 (10%) as Engel II, 5 (10%) as Engel III, and 8 (15%) as Engel IV. Patients were divided into two groups according to outcome: Engel I (excellent outcome) and Engel II–IV.

The duration of follow-up ranged from 1 to 15 years (with an average of 8.3 ± 4.6 years).

3.3. Ictal onset frequency and patterns

We recorded 158 seizures in 51 patients. In all patients, the first detectable changes were present in intracranial electrodes. We excluded 6 seizures from the analysis (5 for artifacts preventing proper interpretation of invasive EEG, 1 for damage of electrodes). The remaining 152 seizures were distributed from 1 to 6 seizures per patient (with average of 3.0 ± 1.1).

We found that 43 (84%) of 51 patients had an exclusive SOP (SIA, FIA, or AT). The other 8 patients were categorized according to their predominant SOP. FIA was present in 34 (67%) patients, SIA in 13 (25%), and AT in 4 (8%) (Fig. 4).

There were no statistically significant differences in patients with different SOPs in terms of age at epilepsy onset, epilepsy duration, or age at time of surgery (Table 2).

3.4. Relationship of SOPs to outcome

We found a borderline statistically significant difference in average frequencies between patients with Engel I outcome and patients with Engel II–IV outcomes. The average frequency was 13.3 ± 6.0 Hz in patients with Engel I and 9.2 ± 7.9 Hz in patients classified as Engel II–IV ($P = 0.081$).

We found that 29 (85%) of the 34 patients with FIA had an Engel I outcome, in comparison with 4 (31%) of the 13 with SIA and 0 (0%) of the 4 AT ($P < 0.001$) (Table 3).

When the FIA patients were subdivided (cut-off value 15 Hz) into two subgroups, 18 patients (53%) had FIA 8–15 Hz and 16 (47%) had FIA > 15 Hz (Table 4). The patients with FIA 8–15 Hz had a better prognosis: 17 (94%) had an Engel I outcome; 12 patients (75%) with FIA > 15 Hz had an Engel I outcome. The difference between these two groups was not statistically significant ($P = 0.164$).

When we subdivided patients with SIA into two subgroups (cut-off value 2 Hz), we saw that 7 (54%) patients had SIA $\leqslant$ 2 Hz and 6 (46%) patients had SIA > 2 Hz (Table 4). SIA $\leqslant$ 2 Hz was associated with a better outcome than SIA > 2 Hz: 4 (57%) patients with SIA $\leqslant$ 2 Hz had an excellent outcome (Engel I), in comparison with 0 (0%) with SIA > 2 Hz, this difference was borderline statistically significant ($P = 0.070$).

3.5. Localization of SOZ, histopathological examination and SOP

SO was characterized as mesial in 38 patients (75%), as temporopolar in 7 (13%), and as laterobasal in 6 (12%). There were no statistical differences in SOZ localization and surgical outcome or SOP (Tables 5 and 6).

In 31 out of 51 patients (60%), extratemporal electrodes were used, which enabled us to study the speed of extratemporal propagation. Three patients with FIA exhibited fast involvement (within 2 s) of the frontal lobe structures. In Table 1, they are numbered as 28, 35, and 48. No patient with SIA showed such fast involvement of the extratemporal structures. In all of the patients with AT, extratemporal electrodes were used. Three out of 4 patients exhibited early widely-distributed and long-lasting attenuation; in the remaining patient with AT, the attenuation was limited to the temporal pole area. After that, rhythmic ictal activity developed; this activity was initially limited to temporal regions and subsequently spread to the extratemporal regions.

A histopathological examination was performed in all 51 patients. The most common pathology was hippocampal sclerosis (HS), which was found in 20 patients (39%); both HS and focal cortical dysplasia (FCD) were found in 2 patients (4%). For further analysis, we grouped these 22 (43%) patients into one group. In 6 patients (12%), isolated FCD was present; all these cases were classified as FCD Ia. Other types of lesion were found in 12 cases (23%): non-specific gliosis in 5, dysembryoplastic neuroepithelial tumor (DNET) in 4, other benign tumors in 2, and a vascular malformation was revealed in 1. In the remaining 11 (22%) patients, the histopathological specimen analysis was negative. There were no statistical differences in histopathological findings and surgical outcome or SOP (Tables 5 and 6), but 10 patients out of 11 (91%) with negative histopathology exhibited FIA.

4. Discussion

Our study shows that patients with refractory TLE caused by different types of lesions exhibit a high grade of SOP uniformity.

Table 1
Main clinical and EEG features in 51 evaluated patients.

Patient No.	Number of seizures	AF (Hz)	Side R/L	Localization of SOZ M/TP/LB	SOP	MRI P/N	Histopathology HS/FCD/NG/OTH	Engel outcome
1	2	8	R	M	FIA	N	NG	I
2	4	NA	R	M	AT	P	HS	IV
3	4	12	L	M	FIA	P	HS	I
4	2	10	L	TP	FIA	P	OTH	I
5	3	2	L	M	SIA	P	FCD	I
6	4	13	L	M	FIA	P	HS	I
7	2	14	R	M	FIA	P	HS	I
8	5	6	L	LB	SIA	P	OTH	IV
9	3	2	R	M	SIA	P	OTH	I
10	5	NA	L	TP	AT	P	FCD	IV
11	4	13	L	M	FIA	P	HS	I
12	1	18	L	M	FIA	N	NG	I
13	1	10	L	M	FIA	P	OTH	I
14	3	5	L	LB	SIA	N	FCD	IV
15	2	13	L	LB	FIA	P	OTH	I
16	6	13	R	M	FIA	P	HS	I
17	3	18	R	M	FIA	P	OTH	I
18	4	5	L	M	SIA	P	HS	I
19	4	20	L	M	FIA	P	HS	II
20	3	16	R	M	FIA	N	FCD	I
21	7	6	L	M	SIA	P	OTH	IV
22	2	9	L	M	FIA	P	HS	I
23	1	14	L	M	FIA	P	HS	I
24	3	20	R	LB	FIA	P	OTH	I
25	2	20	R	M	FIA	N	NG	I
26	1	NA	R	M	AT	P	HS	II
27	1	25	L	M	FIA	P	HS	I
28	2	23	R	TP	FIA	N	NG	I
29	3	16	R	M	FIA	P	HS	I
30	3	17	R	TP	FIA	N	FCD	III
31	4	2	L	M	SIA	P	OTH	I
32	2	20	R	M	FIA	P	HS	I
33	2	2	R	M	SIA	P	HS	I
34	1	4	R	M	SIA	P	HS	III
35	3	19	R	TP	FIA	N	NG	I
36	5	20	R	M	FIA	P	HS	I
37	2	13	L	M	FIA	N	HS	I
38	7	NA	L	TP	AT	N	NG	IV
39	2	24	R	M	FIA	N	NG	III
40	3	10	R	M	FIA	P	NG	I
41	1	4	R	M	SIA	P	OTH	IV
42	3	2	R	M	SIA	P	HS	II
43	3	14	L	TP	FIA	P	HS	II
44	1	22	L	M	FIA	P	HS	II
45	3	12	R	LB	FIA	N	NG	I
46	4	11	R	LB	FIA	N	NG	I
47	4	9	L	M	FIA	P	OTH	I
48	2	13	R	M	FIA	P	OTH	I
49	2	18	R	M	FIA	N	NG	III
50	6	1	L	M	FIA	P	FCD	IV
51	2	2	L	M	FIA	P	HS	III

AF, average frequency; R, right; L, left; SOZ, seizure onset zone; M, medial; TP, temporopolar; LB, laterobasal; SOP, seizure onset pattern; N, negative; P, positive; HS, hippocampal sclerosis; FCD, focal cortical dysplasia; NG, negative finding; OTH, other type of lesion; NA, not applicable.

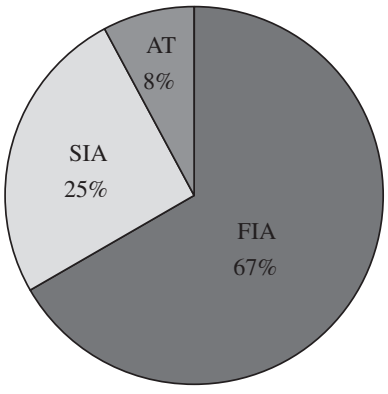

Fig. 4. The percentage representation of individual seizure-onset patters (SOPs).

As defined in our study, 84% of all patients had exclusively only one type of SOP. The literature data show a higher diversity of SOPs in each individual patient. For example, Park et al. (1996) found 49% uniformity of SOP, and Lee et al. (2000) showed 70% uniformity of SOP in an individual patient. This diverse degree of uniformity could be conditioned by the number of seizures per patient (3.0 in our study vs. 4.6 in Park et al. and 6.6 in Lee et al.).

We did not find any relationship between the type of SOP and the demographic characteristics of our patients, i.e. age at epilepsy onset, epilepsy duration, and age at time of surgery. Differences in seizure onset frequencies regarding demographic data have not been described in literature.

The most frequent type of SOP in our patients was FIA, which was present in 67% of patients, followed by SIA (in 25%) and AT (in 8%). This distribution is indirectly comparable to other studies in TLE (Park et al., 1996; Schiller et al., 1998).

Table 2
Relationship of SOP to patient demographic data.

SOP	Mean age at epilepsy onset	Mean duration of epilepsy	Mean age at time of surgery
FIA ($N = 34$)	13.8 ± 7.9	17.5 ± 7.5	30.1 ± 6.7
SIA ($N = 13$)	13.6 ± 7.5	20.2 ± 8.5	33.8 ± 6.3
AT ($N = 4$)	10.5 ± 3.5	17.8 ± 7.6	28.3 ± 7.3
Statistics	$P = 0.837$	$P = 0.719$	$P = 0.432$

SOP, seizure onset pattern; FIA, fast ictal activity; SIA, slow ictal activity; AT, attenuation of background activity.

Table 3
Relationship of SOP to surgical outcome.

SOP	Outcome	
	Engel I	Engel II–IV
FIA ($N = 34$)	29 (85%)	5 (15%)
SIA ($N = 13$)	4 (31%)	9 (69%)
AT ($N = 4$)	0 (0%)	4 (100%)
Statistics	$P < 0.001$	

SOP, seizure onset pattern; FIA, fast ictal activity; AT, attenuation of background activity.

Table 4
More detailed division of FIA and SIA and their relations to surgical outcome.

SOP	Outcome	
	Engel I	Engel II–IV
FIA 8–15 Hz ($N = 18$)	17 (94%)	1 (6%)
FIA > 15 Hz ($N = 16$)	12 (75%)	4 (25%)
Statistics	$P = 0.164$	
SIA $\leqslant$ 2 Hz ($N = 7$)	4 (57%)	3 (43%)
SIA > 2 Hz ($N = 6$)	0 (0%)	6 (100%)
Statistics	$P = 0.070$	

SOP, seizure onset pattern; FIA, fast ictal activity; SIA, slow ictal activity.

In a study by Park et al. (1996) characterized SOs of patients with refractory non-lesional TLE into three patterns (rhythmic activity, repetitive epileptiform discharges, and attenuation of background activity), or their combination. In Park et al. (1996), 49% of the patients had a uniform type of SOP: rhythmic activity was present in 38% of cases and repetitive epileptiform discharges in 11%. Among seizures with rhythmic activity, 83% occurred in the alpha or beta range; the remaining 17% were in the theta or delta range. This result correlates with the representation of FIA and SIA in our study.

In a study by Schiller et al. (1998), SOPs were distributed in mesial TLE (MTLE) and in neocortical TLE (NTLE) as follows: early beta buzz (rhythmic discharges in beta range) in 48% of MTLE and in 74% of NTLE, rhythmic sharp activity in the alpha–theta range in 28% of MTLE and in 15% of NTLE, rhythmic sharp wave activity in the delta range in 20% of MTLE and in 11% NTLE, and irregular or semi-rhythmic spikes and sharp waves in 4% of MTLE; this pattern was not found in NTLE. The first two patterns (i.e. early beta buzz and rhythmic sharp activity in the alpha theta range) reflect FIA in our study; the second two patterns (i.e. rhythmic sharp wave activity in the delta range and irregular/semi-rhythmic spikes and sharp waves) reflect SIA.

Most previous studies analyzing SOPs in TLE divide them into HYP and LVF; these two ictal onsets patterns are defined by their frequency and amplitude and are present in 70–80% of patients (Engel et al., 1989; Engel, 1990; Velasco et al., 2000; Ogren et al., 2009). The remaining 20–30% of patients cannot be classified according to those criteria; for this reason we used different SOP criteria in our study.

FIA at least partially corresponds with LVF, which is defined as high-frequency (>10 Hz), low amplitude discharges (Spencer, 1998; Velasco et al., 2000). HYP was defined as a preictal phenomenon of low frequency ($\leqslant$2 Hz) long-lasting ($\geqslant$5 s) spiking and was described as the most frequently encountered pattern in MTLE, in approximately 50% cases (Engel et al., 1989; Velasco et al., 2000). In our study, HYP can correlate with SIA $\leqslant$ 2 Hz, but this pattern was present in 18% of our patients. This discrepancy in percent representation of SIA $\leqslant$ 2 Hz can be explained by certain characteristics

Table 5
Relationship of surgical outcome to localization of SOZ and to histopathological findings.

Outcome	Localization of SOZ			Histopathology			
	Mesial	Temporopolar	Laterobasal	HS	FCD	Negative	Other
Engel I ($N = 33$)	26 (79%)	3 (9%)	4 (12%)	14 (43%)	2 (6%)	8 (24%)	9 (27%)
Engel II–IV ($N = 18$)	12 (67%)	4 (22%)	2 (11%)	8 (44%)	4 (22%)	3 (17%)	3 (17%)
Statistics	$P = 0.878$			$P = 0.362$			

SOZ, seizure onset zone; HS, hippocampal sclerosis; FCD, focal cortical dysplasia.

Table 6
Relationship of SOP to localization of SOZ and to histopathological findings.

SOP	Localization of SOZ			Histopathology			
	Mesial	Temporopolar	Laterobasal	HS	FCD	Negative	Other
FIA ($N = 34$)	25 (74%)	5 (15%)	4 (12%)	15 (44%)	2 (6%)	10 (30%)	7 (20%)
SIA ($N = 13$)	11 (85%)	0 (0%)	2 (15%)	5 (39%)	3 (23%)	0 (0%)	5 (38%)
AT ($N = 4$)	2 (50%)	2 (50%)	0 (0%)	2 (50%)	1 (25%)	1 (25%)	0 (0%)
Statistics	$P = 0.120$			$P = 0.158$			

SOP, seizure onset pattern; SOZ, seizure onset zone; FIA, fast ictal activity; SIA, slow ictal activity; AT, attenuation of background activity; HS, hippocampal sclerosis; FCD, focal cortical dysplasia.

of HYP and by the IEEG indication criteria of individual centers. First, seizures beginning with HYP tend to remain confined to the epileptogenic region, failing to propagate outside the ipsilateral hippocampus, or doing so only after an extended period of seconds or even several minutes, and after transitioning to another type of ictal discharge (Lieb et al., 1987; Engel, 1996; Bragin et al., 1999). Second, HYP is present in "advanced" grades of HS (Bratz, 1899; Townsend and Engel, 1991; Spencer et al., 1992a; Velasco et al., 2000). Third, only unilateral hippocampal impairment is found on MRI in HYP patients (Ogren et al., 2009). On the basis of these HYP characteristics, we can speculate that our patient's noninvasive data was sufficiently conclusive for us to perform surgery without an IEEG, whereas in other centers, IEEG would be required in these cases.

We found a borderline significant difference in average seizure onset frequency between patients classified as Engel I and Engel II–IV (13.3 Hz vs. 9.2 Hz). This is because patients with seizure onset frequency between 8 and 15 Hz tend to have the best prognosis; frequencies from both higher and lower ranges were associated with worse surgical results. FIA, especially at frequencies between 8 and 15 Hz, was generally associated with an excellent outcome. 85% of patients with FIA (95% with FIA = 8–15 Hz, 75% with FIA > 15 Hz) were classified as Engel I. This observation is in concordance with previously published studies with subdural (Weinand et al., 1992) and epidural (Faught et al., 1992) electrodes, which showed that seizure onset frequencies higher than 8 Hz are associated with good surgical outcomes.

We see a contradiction between the excellent outcome of our patients with FIA and the results of previously published studies by Lin et al. (2007) and by Ogren et al. (2009). In many patients with TLE who exhibit LVF, Lin et al. found significant damage of neocortical areas together with hippocampal atrophy. Ogren et al. (2009) observed significant bilateral hippocampal atrophy on MRI in LVF patients. Ogren et al. suggested two possible explanations for these observations. The first explanation is based on the high tendency of LVF to quickly propagate to the frontal lobes and the contralateral temporal lobe (Lieb et al., 1981; Spanedda et al., 1997; Velasco et al., 2000). Damage of neocortical areas and contralateral hippocampal atrophy could result from long-term exposure to propagated ictal activity. Alternatively, these findings could reflect the presence of undetected secondary epileptogenic regions. Considering our results, we are more inclined to the first suggestion. From another point of view, this study included only patients who had surgery after IEEG. Patients with extensive damage of both hippocampi, with bitemporal epilepsy, or with non-conclusive IEEG data are less likely to have surgical treatment.

In our study, patients with SIA had worse outcomes: only 30% were classified as Engel I. This difference cannot be explained by the involvement of extratemporal structures. Firstly, patients with contemporary involvement of both temporal and extratemporal structures were not included in our study. Secondly, the very fast involvement of extratemporal structures in the ictal process was present only in patients with FIA, and all these patients were classified as Engel I. Patients with SIA $\leqslant$ 2 Hz tended to have better outcomes than patients with SIA > 2 Hz. More than 50% of patients with SIA $\leqslant$ 2 Hz had an excellent outcome; this pattern corresponds with HYP as defined above. None of our 6 patients with SIA > 2 Hz had an excellent outcome. This pattern is consistent with rhythmic theta–delta activity, which was described by Schiller et al. (1998) as a unique pattern of electrographic seizure propagation and indicates that the epileptogenic zone remains uncovered by the intracranial electrodes.

Only a limited number of studies have emphasized the AT pattern and its significance (Wieser and Siegel, 1991; Gotman, 1999; Alarcon et al., 1995; Wendling et al., 2003). Electrodecremental events involve high-frequency activity between 20 and 80 Hz. In our study, these events were widely distributed and long-lasting, subsequent clear-cut rhythmic activity evolved initially in temporal regions and then later in extratemporal regions as well. We have two possible explanations for the association between AT and worse outcome (no patient was classified as Engel I; moreover, 3 out of 4 AT patients were classified as Engel IV), although these explanations cannot be generalized because of the small sample size. The first explanation is that AT could reflect extratemporal seizure origin with preferential propagation of ictal activity to the temporal lobe structures. The second explanation is based on the work of Alarcon et al. (1995). He supposed that electrodecremental events are not a part of the ictal process itself, but reflect generalized cerebral changes that allow particularly susceptible regions to develop paroxysmal behavior that gradually recruits neighboring regions. Alarcon et al. postulated that partial seizures can begin in regions that are prone to generate paroxysmal ictal activity in response to previously described generalized electrical changes.

We did not find any statistically significant relations between SOPs and localization of SOZ or histopathological findings.

Most (more than 70%) SOPs were distributed in the mesial temporal regions. In the literature, the differences between LVF and HYP onset patterns in SOZ locations are delineated. LVF is found more often in patients with extrahippocampal ictal onset (Engel, 1996, 2001). Bragin et al. (2005) found that the peak amplitudes of LVF onsets are located in the lateral temporal lobe indicating neocortical ictal onsets. In our group of patients with laterobasal SOZ, FIA was present in almost 70%, but this result may be influenced by the small sample size. HYP has been reported to be the most common pattern in patients with MTLE (Engel et al., 1989; Velasco et al., 2000). We did not observe SIA $\leqslant$ 2 Hz, which correlates with this pattern so frequently (in 18% of patients with MTLE).

In our study, 44% of patients with FIA and 40% of patients with SIA had HS. Several histopathological and MRI studies have focused on detailed HS characterization and on the delineation of HS differences by use of HYP and LVF onset patterns. According to histopathological studies, hippocampal cell loss is typically found to be greater in HYP patients than in LVF patients, but this observation was not confirmed by MRI studies. In HYP patients, the cell loss is predominantly localized in areas CA1, CA3, CA4, dentate gyrus, and prosubiculum of hippocampus, sparing area CA2, which is the picture of "classical" HS (Bratz, 1899; Townsend and Engel, 1991; Spencer et al., 1992a,b; Velasco et al., 2000; Ogren et al., 2009). In contrast, Ogren et al. (2009) found extensive damage of area CA2 in patients with LVF. Velasco et al. (2000) showed greater or equivalent cell loss in CA2 compared to all hippocampal subfields, except CA1, in patients with LVF. This atypical distribution of damage in the LVF group appears more diffuse than "classical" HS and may indicate a more diffuse temporal lobe disorder distinct from classical HS (Ogren et al., 2009). We are not able to determine retrospectively a sufficiently detailed and precise histopathological data to define the differences between FIA and SIA in distribution of hippocampal atrophy, which is one of the limitations of our study.

The association of FIA and negative histopathological finding is interesting and quite challenging to interpret. Negative histopathological findings are common, appearing in more than 50% of samples in a group of MRI negative, PET positive patients, which is a group of patients with good surgical outcome (Carne et al., 2004; Immonen et al., 2010). In our group, 8 out of 11 patients (73%) with negative histopathological findings had an excellent outcome; probably some could have been categorized as MRI negative, PET positive, but PET was performed only in patients after 2005. In this context, we can hypothesize that the association of FIA and negative histopathology could reflect favorable prognosis for these patients.

In our study, we did not find any relations between surgical outcome and SOZ localization or histopathological findings, but this result could be influenced by indication criteria for IEEG and patient selection. We explored patients with HS only if there were discrepancies in their clinical and/or non-invasive data. On the other hand, almost all patients with negative MRI findings underwent IEEG in the past, although they would now be categorized as MRI-negative, PET-positive TLE and would have surgery on the basis of their non-invasive data (Kuba et al., 2011; LoPinto-Khoury et al., 2011).

We see some technical deficiencies in our study. The first is the 128 Hz sampling rate of our EEG monitoring system; this sampling rate does not allow us to study high frequency oscillations (HFOs), i.e. frequencies between 80 and 500 Hz. Both ictal and interictal HFOs are specific to areas of seizure generation, which is supported by the correlation between the surgical removal of tissue-generating HFOs and a good surgical outcome (Akiyama et al., 2011; Jacobs et al., 2009, 2010; Nariai et al., 2011; Ochi et al., 2007; Wu et al., 2010). The increase of HFOs was found during the seconds preceding the SO, during intrinsic SO, and during the propagation of ictal activity; these preictal and ictal HFOs are thought to be more specific for the SOZ than interictal HFOs (Allen et al., 1992; Fisher et al., 1992; Jirsch et al., 2006; Khosravani et al., 2009; Nariai et al., 2011; Zijlmans et al., 2011). The second technical limitation is that we did not provide a relationship between ictal activity and interictal activity, used as a resting state; this process would enable the analysis of higher frequencies than low beta activity. On the other hand, this method is not common in the daily praxis of epilepsy centers, and the main purpose of this work was to provide a helpful patient evaluation tool for clinicians, both epileptologists and neurophysiologists. It is a challenge to perform an analogous study with more detailed processing of ictal, preictal, and postictal data, and with a higher number of patients; such a study could provide a useful standard to the decision-making process about surgery.

Our data suggests that SOP in IEEG could be an independent predictive factor for surgical outcome in patients with TLE. Higher frequencies, as a first change in IEEG, indicate better surgical outcomes, and we could hypothesize that they are associated with initial electrographic changes of seizure onsets. Slower frequencies, especially between 3 and 8 Hz, imply worse surgical outcome and could be linked with the propagation of seizure activity.

Acknowledgments

We thank Anne Johnson for grammatical assistance. This work was supported by the "CEITEC – Central European Institute of Technology" Project (CZ.1.05/1.1.00/02.0068) from the European Regional Development Fund. The study was supported by Grant GACR P304/11/1318.

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Annex 4: Pail M, Rehulka P, Cimbalnik J, **Dolezalova I**, Chrastina J, Brazdil M. Frequency-independent characteristics of high-frequency oscillations in epileptic and non-epileptic regions. Clinical Neurophysiology. 2017;128(1):106-114.

Clinical Neurophysiology 128 (2017) 106–114

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Frequency-independent characteristics of high-frequency oscillations in epileptic and non-epileptic regions

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ARTICLE INFO

Article history:
Accepted 15 October 2016
Available online 29 October 2016

Keywords:
High frequency oscillations
Ripples
Fast ripples
Temporal lobe epilepsy
Extratemporal lobe epilepsy
Seizure onset zone
Epileptogenic zone
Irritative zone

HIGHLIGHTS

- The highest rate of fast ripples is in the seizure onset zone (SOZ).
- A worse prognosis (no seizure freedom after surgery) is associated with higher amplitudes of fast ripples outside the SOZ.
- In the SOZ, high frequency oscillations are more frequent, shorter, and have higher amplitudes.

ABSTRACT

Objective: The purpose of the presented study is to determine whether there are frequency-independent high-frequency oscillation (HFO) parameters which may differ in epileptic and non-epileptic regions.
Methods: We studied 31 consecutive patients with medically intractable focal (temporal and extratemporal) epilepsies who were examined by either intracerebral or subdural electrodes. Automated detection was used to detect HFO. The characteristics (rate, amplitude, and duration) of HFO were statistically compared within three groups: the seizure onset zone (SOZ), the irritative zone (IZ), and areas outside the IZ and SOZ (nonSOZ/nonIZ).
Results: In all patients, fast ripples (FR) and ripples (R) were significantly more frequent and shorter in the SOZ than in the nonSOZ/nonIZ region. In the group of patients with favorable surgical outcomes, the relative amplitude of FR was higher in the SOZ than in the IZ and nonIZ/nonSOZ regions; in patients with poor outcomes, the results were reversed. The relative amplitude of R was significantly higher in the SOZ, with no difference between patients with poor and favorable surgical outcomes.
Conclusions: FR are more frequent, shorter, and have higher relative amplitudes in the SOZ area than in other regions. The study suggests a worse prognosis in patients with higher amplitudes of FR outside the SOZ.
Significance: Various HFO parameters, especially of FR, differ in epileptic and non-epileptic regions. The amplitude and duration may be as important as the frequency band and rate of HFO in marking the seizure onset region or the epileptogenic area and may provide additional information on epileptogenicity.

1. Introduction

Over the past few years, there has been growing interest in the analysis of interictal high frequency oscillations (HFO), primarily with the goal of understanding their value for identifying the epileptogenic zone and their correlation with epileptogenicity. HFO promise to be more specific than interictal spikes for epileptogenic brain tissue and even more specific than the seizure-onset area (Jacobs et al., 2008).

HFO are short-lasting field potentials, which arise as a result of the synchronization of neuronal populations. HFO have been identified and defined in terms of frequency: ripples (80–250 Hz), fast ripples (250–600 Hz) (reviewed in Bragin et al., 2010; Engel et al.,

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http://dx.doi.org/10.1016/j.clinph.2016.10.011
1388-2457/

2009), and very high frequency oscillations (1000–2500 Hz) (Usui et al., 2015). HFO have been widely studied in animals and humans, in mesial temporal and neocortical structures, under physiological and pathological conditions, using microelectrodes or commercial macroelectrodes, and during interictal and ictal periods (Bragin et al., 1999a,b; Staba et al., 2002; Worrell et al., 2004, 2008; Urrestarazu et al., 2007; Jacobs et al., 2008, 2009; Bagshaw et al., 2009; Brázdil et al., 2010; Crépon et al., 2010). However, the reliability of HFO as a biomarker of epileptogenicity and the seizure-onset zone remains uncertain (Haegelen et al., 2013; Jobst, 2013; Wang et al., 2013).

Ripples, observed as a physiological finding in the hippocampus and parahippocampal structures, are thought to be functionally involved in memory consolidation (Buzsáki et al., 1992; Axmacher et al., 2010; Lachaux et al., 2012). The spontaneous occurrence of ripples in humans is also believed to be physiological in the primary visual cortex (Nagasawa et al., 2012; Wang et al., 2013) and in the primary motor cortex (Wang et al., 2013). The presumption of the exclusively physiological nature of ripples was, however, impugned by evidence of HFO in ripple ranges recorded in the dentate gyrus after epileptogenic insult in an animal model of kainate-induced status epilepticus (Bragin et al., 1999b, 2004).

Conversely, fast ripples were repeatedly reported as a biomarker of epileptogenesis and epileptogenicity, both in animal models and in human epilepsy (Bragin et al., 1999a,b; Staba et al., 2002). It is important that HFO in the fast ripple range (at about 600 Hz) can also be considered physiological, as they were previously evoked during stimulation of the somatosensory cortex (Curio et al., 1997). Thus the HFO frequency range, in general, is not sufficient to differentiate physiological and pathological HFO (Bragin, 2007). On the other hand, there is evidence of favorable epilepsy surgery outcome after the removal of tissue generating interictal HFO, especially fast ripples (Jacobs et al., 2010; Wu et al., 2010; Akiyama et al., 2011).

Several authors have tried to distinguish between pathological and physiological HFO on the basis of a specific regional distribution in respective mesial temporal structures (Jiruska and Bragin, 2011); some have investigated the difference between task-induced and spontaneous HFO (Nagasawa et al., 2012; Matsumoto et al., 2013; Brázdil et al., 2015); others have studied the association of HFO with epileptiform discharges (Crépon et al., 2010; Urrestarazu et al., 2007; Wang et al., 2013). Interictal HFO (both ripples and fast ripples) rates were proven significantly higher within the seizure onset zone (SOZ) than outside it (Jacobs et al., 2009).

The purpose of the present study is to identify whether there are any other frequency-independent HFO parameters that potentially differ in areas within the SOZ, within the irritative zone (IZ), and in areas outside the IZ/SOZ.

2. Methods

2.1. Subjects

Our sample comprised 31 patients (19 females; 12 males) ranging in age from 13 to 56 years (mean age 33.4 years, SD = 10.5), all with medically intractable focal epilepsies (Table 1). All the subjects fulfilled the diagnostic criteria for either medically intractable temporal lobe epilepsy (TLE) – 22 subjects or extratemporal lobe epilepsy (ETLE) – 9 subjects. The diagnosis was made according the ILAE criteria (Commission on Classification and Terminology of ILAE, 1989). The main demographic and clinical characteristics of the included subjects are shown in Table 1.

2.1.1. Presurgical evaluation

All 31 patients underwent a comprehensive presurgical evaluation, including a detailed history and neurological examination, magnetic resonance imaging (MRI), neuropsychological testing, and scalp and invasive video-EEG monitoring (Table 1). Most of the subjects had not previously undergone intracranial surgery. One subject underwent resection of venous malformation within the left P-O region before SEEG and re-operation; in one subject a resection of the pole of the left temporal lobe had been performed, and in one subject a limited left AMTR was performed before SEEG monitoring. Prior to invasive EEG, two subjects had a vagus nerve stimulation system implanted, with unfavorable seizure frequency outcome. The duration of clinical monitoring and the location and number of implanted electrodes were determined in accordance with clinical considerations.

2.1.2. Surgery and outcome measure

Most of the patients (28) underwent surgical intervention (implantation of VNS was performed in 7 patients and brain resection in 21 patients; details are shown in Table 1). The follow-up interval after epilepsy surgery was at least 12 months. After surgical resection, 8 patients were rated as Engel IA, one patient was Engel IIA, and 11 patients were Engel III or IV; the Engel rating is unknown for one patient (due the loss to follow-up care).

This study was approved by the St. Anne's University Hospital Research Ethics Committee and the Ethics Committee of Masaryk University. All patients signed an informed consent form.

2.2. SEEG

Depth electrodes (mostly SEEG; grids and strips were used in two patients) were implanted to localize the seizure origin prior to surgical treatment. The sites of electrode placements were individualized according to seizure semiology, clinical history, noninvasive EEG investigations, and neuroimaging results. Standard intracerebral 5-, 10-, and 15-contact Micro Deep semi-flexible multicontact platinum electrodes (ALCIS) were used with a diameter of 0.8 mm, a contact length of 2 mm, an inter-contact distance of 1.5 mm, and a contact surface area of 5 mm^2. Their position within the brain was afterwards verified by MRI with electrodes in situ (see Table 1). In two patients, platinum subdural strip and grid electrodes (Radionics) were used. Thirty minutes of artifact-free continuous interictal SEEG data (recorded during wakefulness) was analyzed for each subject. This period is sufficient based on the results of previously published papers (Jacobs et al., 2008; Zelmann et al., 2009; Andrade-Valença et al., 2012). The EEGs were acquired at 25 kHz sampling frequency and subsequently low-pass filtered and downsampled to 5 kHz. High harmonics produced by the system (artificial harmonics) are accounted for during EEG acquisition. A reference average montage was used for the analysis.

2.2.1. Labeling of analyzed contacts

The contacts in each subject were divided into three groups for further HFO analysis. The distribution was done visually (by co-authors M.P. and I.D.) by a standard analysis of ictal and interictal SEEG recordings. The first group was labelled SOZ contacts: the channels that revealed the first ictal activity. The second group was labelled IZ contacts: the channels where interictal epileptiform discharges were detected, but no seizure onset was detected. The remaining non-spiking contacts were labelled nonSOZ/nonIZ. Only contacts localized in gray matter were included in the study.

2.2.2. Automated detection of HFO in resting awake SEEG

The algorithm for HFO detection is explained in more detail in the Supplementum. HFO were detected by a custom Matlab detection algorithm. The raw signal (Supplementary Fig. S1) was divided

Table 1
Demographic and clinical data of the patients.

Subject gender	Age at seizure onset	Age at invasive EEG	Seizure frequency/monthly	Febrile seizures/precipitating events	MRI (signs of)	Brain lobes explored and number of implanted electrodes	Region SOZ (epileptogenic zone)	Intervention/histopathology	Postsurgical outcomes (Engel) (years)
1 (F)	16	20	CPS/4plus	0	Normal	T (3), T′(2)	H bilaterally	VNS	–
2 (F)	19	57	CPS/2plus, sGTCS/6	0	Postischemic lesions within left T-O and H	F′(1), T′(5)	Left H	AMTR/gliosis, hemosiderin within T pole	IA (3.5)
3 (F)	4	34	CPS/50	0	Hypotrophic right H	T′(3), T(3)	Right H	AMTR/hippocampal sclerosis grade III	IA (3.5)
4 (F)	6	19	CPS/4	Perinatal hypoxia	Gliosis and cortical abnormalities left PO	O′(2), T′(2), P′(1), O(2), F(2)	Left TPO region	Cortectomy/negat	IV (3)
5 (F)	2	34	SPS,CPS/4	Perinatal asphyxia	Polymicrogyria left F, postoperative changes of left PO	F′ (8), P′(2), T′(1)	Left P lobe, pericentral area	VNS	–
6 (F)	16	33	CPS/5	Perinatal hypoxia	Bilat. HS	T′(4), T(4)	H bilaterally (mainly right side)	Right AMTR/negat	III (2.5)
7 (M)	0.5	21	CPS/30, MS/300	0	Abnormality of left H	F′(9), P′(1), T′(1), F(2)	Left SMA (myoclonic seizures), left F pole (CPS)	Resection of left F pole/negat	IV (2.5)
8 (F)	9.5	13	CPS/30	Perinatal asphyxia	Malrotation of left H	P′(5), T′(5), F′(1), O(1), P(1)	Undetected	–	–
9 (M)	9	27	CPS/30 plus	Perinatal asphyxia	Bilat. abnormal gyrification and gliotic changes of PO	O (2), T (3), P(3), O′(3), T′(1), P′(3)	O lobe bilaterally (mainly right side)	Partial resection of right O lobe/ ulegyria, FCD IIIA	IIIA (2)
10 (F)	9	30	CPS/3	Perinatal asphyxia	Normal	T (3), T′(8), O′(2)	Left lateral T lobe, GTS	Incomplete resection of left GTS/ negat	IVA (2)
11 (F)	17	26	CPS/12	Meningoencephalitis	Normal	T (1), T′(8)	Lateral mesial T lobe	Left AMTR/FCD IB	IA (2)
12 (F)	28	56	CPS/8	0	Right hippocampal sclerosis	T (2), T′(3)	Right H	Right AMTR/negat	IIIA (2)
13 (M)	1	40	CPS/2 plus	0	Hypotrophic left H	T′(6), P′(2), O′(2)	Left H	Left AMTR/negat	IA (2)
14 (F)	11	27	sGTCS/3	0	Normal	F(4), F′(8)	Left GFS, GFM, GFMed	Partial cortectomy of left F lobe	IIIA (2)
15 (M)	19	26	CPS/4	0	FCD left T and hyperintensity of H	T′(7), F′(1), T (1)	Left anterotemporal, right mesial temporal	VNS	–
16 (F)	10	34	SPS, CPS/10 plus	Perinatal asphyxia	Normal	F′(5), P′(2), F(6), P(2)	Right dorsolateral parasagittal premotoric area	Partial cortectomy of right F lobe, partial callosotomy/FCD 1C	Not available
17 (M)	27	38	CPS/25 plus	0	Normal	T(3), I′(2), T′(6), P′(1), O′(1), F′(1)	Mesial T region bilaterally	VNS	–
18 (F)	6	48	CPS/60 plus	Febrile seizures	Postoperative gliosis right P	P(6), T(3), O(1)	Right TP cortex, right hippocampus	VNS	–
19 (M)	33	41	CPS/30	0	Focal hyperintensity right basal T	T(4), T′(3)	Right H	Right AMTR/FCD IIIb gangliogliom	IA(1.5)
20 (M)	11	25	CPS/12 plus	0	Normal	TPO grids	Right lateral T lobe	Cortical resection of right T a TO region/negat	IIA(2)
21 (F)	17	40	CPS/20	0	Normal	F′(1),O′(2),T′(7),T(2)	Undetected	–	–
22 (F)	17	40	CPS/20	0	Normal	FTPO′ grids	Left laterobasal posterior T lobe	Cortectomy of left laterobasal posterior T lobe/negat	IIIA (1.5)
23 (M)	8	29	CPS/20 plus	0	Normal	T′(7), F′(2), T(2)	Bitemporal	Left AMTR/negat	IVA (1)
24 (F)	2	33	CPS/6 plus	Meningoencephalitis	Postencephalitic changes left T	T(2), T′(6), F′(3)	Left H	Left AMTR/hippocampal sclerosis, postmeningoencephalitic changes	IA (1)
25 (M)	12	40	CPS/40 plus	Trauma	Posttraumatic changes of left T and GFI	F′(6), T′(5)	Left T pole, lateral T, lateral prefrontal area	Resection of temporal pole, lesionectomy F left/posttraumatic changes	IIIA (1)
26 (F)	2	33	sGTCS/10	0	Postoperative changes right PO	T(3), P(2), O(2)	Right GTS, LPI	–	–
27 (F)	2	22	CPS/4	0	Postoperative changes right PO	P(2), F(2), T(3)	Undetected (right posterior quadrant)	VNS	–

Table 1 (*continued*)

Subject gender	Age at seizure onset	Age at invasive EEG	Seizure frequency/monthly	Febrile seizures/precipitating events	MRI (signs of)	Brain lobes explored and number of implanted electrodes	Region SOZ (epileptogenic zone)	Intervention/histopathology	Postsurgical outcomes (Engel) (years)
28 (M)	21	35	CPS/5	Commotio cerebri	Bilat. hypotrophic hippocampi	T(6), T′(2)	H bilaterally (mainly right side)	VNS	–
29 (M)	31	37	CPS/4	Prolonged febrile seizures	Normal	T′(8), F′(2), T(2)	H bilaterally (mainly left side)	Left AMTR/negat	IA (1)
30 (F)	9	27	CPS/5	Meningoencephalitis	Left HS	T′(8), T(2), P′(1), I′(1), F′(1)	Left H	Left AMTR/FCDIIIA	IIIA (1)
31 (M)	2	51	CPS/3 plus	Febrile seizures	Right H atrophy, slight changes of density	T(5), F(3), T′(2)	Right H	Right AMTR/negat	IA (1)

CPS – complex partial seizure; MS – myoclonic seizures; plus – sporadic ictal generalization; SOZ – seizure onset zone; SMA – supplementary motor area; LPI – lobulus parietalis inferior; GTS – gyrus temporalis superior; GFS – gyrus frontalis superior; GFM – gyrus frontalis medius; GFMed – gyrus frontalis medius; H – hippocampus; HS – hippocampal sclerosis; DNET – dysembryoplastic neuroepithelial tumor; FCD – focal cortical dysplasia; AMTR – anteromedial temporal resection; E – extratemporal; T – temporal; R – right; L – left; FCD – focal cortical dysplasia; F – frontal; P – parietal; T – temporal; O – occipital, I – insular; ′ - left.

into sliding statistical windows (10 s) and filtered in a series of overlapping, logarithmically spaced frequency bands. Each band was processed as follows:

The power envelope was computed using the Hilbert transform and normalized by Eq. (1) to stress the signal peaks (Supplementary Fig. S2).

$$x_{normed} = \frac{x - P_{2/3}}{P_{1/3} - P_{2/3}} \quad (1)$$

To overcome the effects of Gibb's phenomenon, a "frequency stability" metric was computed. The band passed filtered signal (narrow band) was transformed to a cosine representation of its phase. The same transformation was applied to a band passed filtered signal with the same high cut-off frequency but a four times lower low cut-off frequency (broad band) (Supplementary Fig. S3a, b). A sliding window with the width of four cycles of the narrow band low cut-off frequency was applied to the narrow band signal and the root mean square (RMS) was calculated, thus generating the "signal". Similarly, the RMS was calculated on the signal created by subtracting the narrow band signal from the broad band signal, generating "noise". The frequency stability was calculated as a "signal-to-noise" ratio. The produced signal was normalized Eq. (1).

The dot product of the amplitude and frequency stability metric was calculated. Negative values were set to 0. Putative HFO detections were obtained by thresholding the normalized Eq. (1) dot product of the power envelopes and frequency stability with 0.1 (Supplementary Fig. S4).

To increase algorithm specificity, amplitude, and frequency stability, the dot product and duration minimum/maximum thresholds were applied on putative HFO detections. The metric threshold values were obtained from cumulative distribution functions fitted to the HFO metric distributions previously marked by expert reviewers. The parameters of the fitted gamma functions were specific for each band. The parameters (Supplementary Table S1) and examples of true positive detection and false positive detection (Supplementary Fig. S5) are included in the Supplementum.

2.3. Statistical analysis

The rates of HFO per contacts within the three groups (SOZ, IZ, and nonSOZ/nonIZ) were statistically compared (SOZ × IZ; SOZ × nonSOZ/nonIZ; IZ × nonSOZ/nonIZ). This statistical analysis was performed using an independent two sample *t*-test separately for ripple range and fast ripple range. We performed statistical analyses on the whole dataset and separately for patients with favorable postoperative outcomes (Engel I or II – 9 patients) and the other patients with "poor outcomes" (postsurgical outcomes of Engel III or IV and patients with presumed poor outcomes due to more than one detected SOZ according to SEEG). Furthermore, we performed a statistical analysis comparing the duration and relative amplitude of HFO (separately for R and FR ranges) for contacts in the areas, as defined above. This analysis was performed in all patients and subsequently in patients with favorable or poor surgical outcomes. For this analysis, we again used an independent two sample *t*-test. Bonferroni's correction for multiple comparisons was applied where needed.

3. Results

The statistical analysis and complete results of HFO detection (rates, duration, and amplitudes) are shown in Table 2 and Supplementary Table S2, respectively.

3.1. Rates

As expected, the HFO rate per contact in all patients was statistically higher in the SOZ than in the nonSOZ/nonIZ regions (Fig. 1) in the fast ripple frequency range ($p = 0.018$) and ripple range ($p = 0.038$).

Specifically, HFO in the ripple range were identified. The mean number of HFO per contact (per 30 min) was 109.13 within the SOZ (SD = 79.19), 96.03 in the IZ (SD = 82.24) and 68.65 for nonSOZ/nonIZ regions (SD = 49.24). The differences between groups of contacts were significant only between SOZ and nonSOZ/nonIZ regions. In the fast ripple range, the mean HFO count per contact (per 30 min) were 50.02 in the SOZ (SD = 50.75), 31.56 in the IZ (SD = 34.89) and 23.23 in nonSOZ/nonIZ (SD = 21.84). The only significant result was in the comparison of SOZ and nonSOZ/nonIZ regions; see above.

No statistically significant results were seen in comparison of regions separately in groups of patients with favorable or poor outcomes.

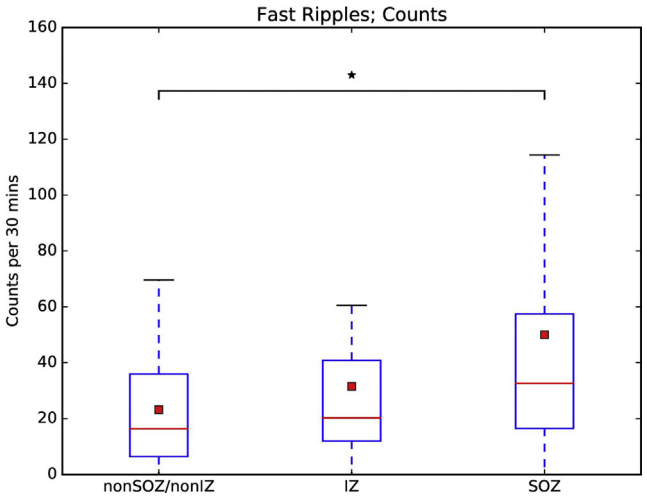

Fig. 1. Counts of fast ripples per 30 min in particular areas (SOZ, IZ, and nonSOZ/nonIZ) in all patients.

3.2. Duration

3.2.1. Ripples

The mean duration of detected HFO was 54.40 ms in the SOZ (SD = 25.58), 56.31 ms in the IZ (SD = 27.52) and 56.12 ms in nonSOZ/nonIZ regions (SD = 29.16). Statistical analysis showed significantly shorter durations of HFO in the SOZ than in either the IZ or nonSOZ/nonIZ regions ($p < 0.001$); the difference between the IZ and nonSOZ/nonIZ regions was not significant ($p = 0.361$).

3.2.2. Fast ripples

Similarly, automated detection in the fast ripple range detected the mean durations of HFO of 27.43 ms in the SOZ (SD = 16.04), 29.13 ms in the IZ (SD = 18.30) and 30.41 ms, in nonSOZ/nonIZ regions (SD = 20.94); the shortest durations of FR were in the

Table 2
The results of statistical analysis (two sample *t*-test, *p* values) comparing the rates, duration, and relative amplitudes of HFO (all over separately for ripples [first column] and fast ripples range [second column]) per contacts in the redefined areas (SOZ, IZ, nonSOZ/nonIZ); also in this analysis particularly in all patients and in patients with favorable or poor outcomes.

Rates

	nonSOZ/nonIZ						IZ					
	All		Favorable outcome		Poor outcome		All		Favorable outcome		Poor outcome	
SOZ	0.038	0.018	0.417	0.143	0.102	0.076	1.078	0.228	0.102	0.092	0.974	0.407
IZ	0.245	0.543	1.243	1.136	0.464	0.491	x	x	x	x	x	x
nonSOZ/nonIZ	x	x	x	x	x	x						

Duration

	nonSOZ/nonIZ						IZ					
	All		Favorable outcome		Poor outcome		All		Favorable outcome		Poor outcome	
SOZ	<<0.001	<<0.001	<<0.001	<<0.001	0.877	<<0.001	<<0.001	<<0.001	<<0.001	<0.001	<<0.001	<<0.001
IZ	0.361	<<0.001	<<0.001	0.460	<<0.001	0.027	x	x	x	x	x	x
nonSOZ/nonIZ	x	x	x	x	x	x						

Amplitude

	nonSOZ/nonIZ						IZ					
	All		Favorable outcome		Poor outcome		All		Favorable outcome		Poor outcome	
SOZ	<<0.001	0.430	<<0.001	<<0.001	<<0.001	<<0.001	<<0.001	0.309	<<0.001	0.014	0.030	<<0.001
IZ	<<0.001	0.013	<<0.001	<<0.001	<<0.001	1.136	x	x	x	x	x	x
nonSOZ/nonIZ	x	x	x	x	x	x						

SOZ, HFO durations were longer in nonSOZ/nonIZ regions than in the IZ ($p < 0.001$) and in nonSOZ/nonIZ regions than in the SOZ ($p < 0.001$). The difference between the IZ and SOZ was also significant ($p < 0.001$).

In the group of patients with favorable outcomes, shorter R and FR durations were seen in the SOZ ($p < 0.001$) than in nonSOZ/nonIZ and IZ regions (see Fig. 2).

In the group of patients with poor outcomes, the longest duration of R was in the IZ ($p < 0.001$); the difference between nonSOZ/nonIZ × SOZ was not significant ($p = 0.877$). In both subgroups of patients, the shortest FR duration was seen in the SOZ ($p < 0.001$).

3.3. Amplitudes

3.3.1. Ripples

Automated detection in the ripple range detected the relative amplitudes of HFO in the SOZ of 77.47 (SD = 164.35), in the IZ of 66.14 (SD = 231.74) and in nonSOZ/nonIZ regions of 56.30 (SD = 151.74). Statistical analysis showed significantly higher amplitudes of HFO in the SOZ than in either the IZ or nonSOZ/nonIZ regions ($p < 0.001$); the difference between the IZ and nonSOZ/nonIZ regions was also significant ($p < 0.001$).

3.3.2. Fast ripples

Automated detection in the fast ripple range detected relative amplitudes of HFO in the SOZ of 76.04 (SD = 164.95), in the IZ of 80.93 (SD = 458.49) and in nonSOZ/nonIZ regions of 73.79 (SD = 241.17). The differences between SOZ and IZ or nonSOZ/nonIZ were not significant.

Nevertheless, in the group of patients with favorable outcomes, the relative amplitude of HFO (both R and FR) was higher in the SOZ than in the IZ and nonIZ/nonSOZ region ($p < 0.001$) (see Figs. 3 and 4). In the group of patients with poor outcomes, the highest amplitude of R was seen in the SOZ ($p < 0.001$) (versus nonSOZ/IZ); $p = 0.030$ (IZ) and the lowest in nonIZ/nonSOZ region ($p < 0.001$). The relative amplitude of FR was lower in the SOZ than in either the IZ or nonSOZ/nonIZ regions ($p < 0.001$) (see Fig. 5).

4. Discussion

Interictal HFO analyses in patients with epilepsy have been reported useful for SOZ identification (Urrestarazu et al., 2007;

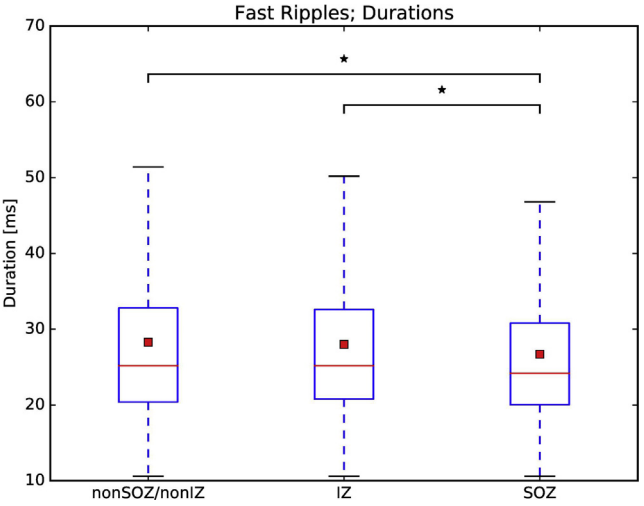

Fig. 2. Durations (ms) of fast ripples in particular areas (SOZ, IZ, and nonSOZ/nonIZ) in patients with favorable outcomes.

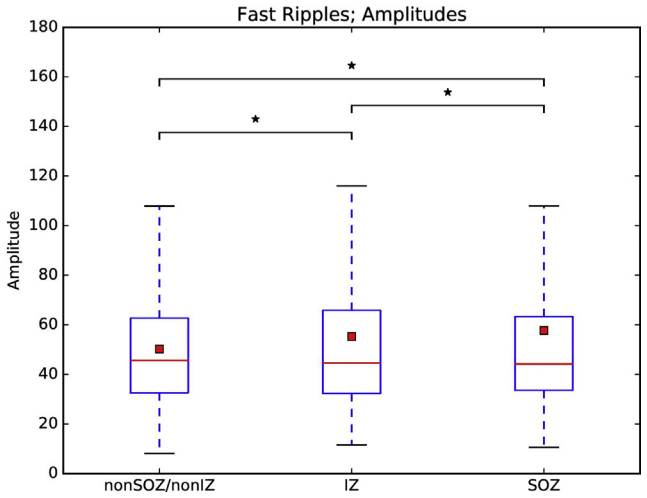

Fig. 3. Relative amplitudes of fast ripples in particular areas (SOZ, IZ, and nonSOZ/nonIZ) in patients with favorable outcomes.

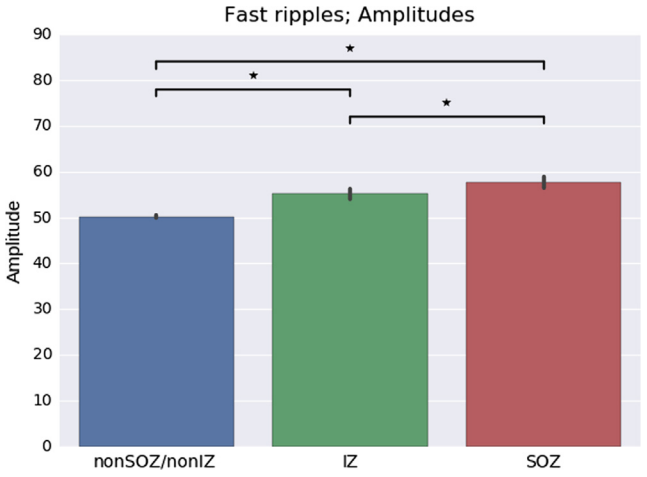

Fig. 4. Relative amplitudes of fast ripples in particular areas (SOZ, IZ, and nonSOZ/nonIZ) in patients with favorable outcomes. Bar graphs represent the population mean. Ticks represent a 95% confidence interval of the mean calculation.

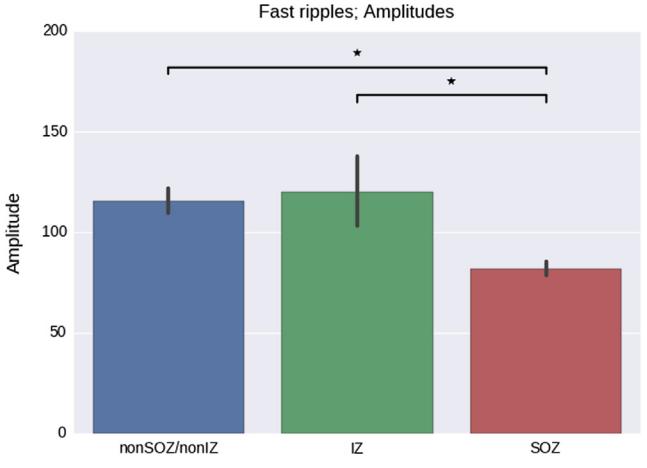

Fig. 5. Relative amplitudes of fast ripples in particular areas (SOZ, IZ, and nonSOZ/nonIZ) in patients with poor outcomes. Bar graphs represent the population mean. Ticks represent a 95% confidence interval of the mean calculation.

Jacobs et al., 2008, 2009). In the present study, patients with both temporal and extratemporal epilepsy were examined to ascertain facts about HFO characteristics in areas within and outside the SOZ and the IZ. For these purposes, we used the concept of an epileptogenic zone (Lüders and Awad, 1992; Rosenow and Lüders, 2001), and used the term "irritative zone" as it has been used elsewhere (Blanco et al., 2011) to investigate HFO characteristics in more detail, to observe the area between the SOZ and non-SOZ, and to eliminate potential overlap of interictal active ("spiking") channels within SOZ and non-SOZ. Only patients who underwent surgical resections and had good postsurgical outcomes reflect the correct determination of the seizure onset zone. For that reason, we divided patients into two subgroups: favorable outcome and others ("poor outcome").

In our study, HFO were detected in all (SOZ, IZ, and nonSOZ/nonIZ) areas, with a higher absolute HFO rate for events in the R range than in the FR range. These findings are not surprising; the occurrence of high frequency activity unassociated with the SOZ is well documented in the hippocampi (Staba et al., 2002; Axmacher et al., 2010) and in the primary motor, somatosensory, and visual cortices (Curio, 2000; Nagasawa et al., 2012; Matsumoto et al., 2013; Wang et al., 2013). The results indicate that the detection algorithm, in addition to detecting pathological HFO, may also detect HFO that might be physiological, might be a fragment or propagation of pathological HFO arising from elsewhere (Crépon et al., 2010), or might be false positive detections. Higher HFO rates in the R range than in the FR range may be explained by an association between HFO and interictal spiking (Urrestarazu et al., 2007; Jacobs et al., 2008; Wang et al., 2013). There is evidence that larger networks are involved in R than in FR generation in SOZ areas (Chrobak and Buzsáki, 1996; Bragin et al., 2002) and that FR generators are spatially localized to a region of less than 1 mm^3 (Bragin et al., 2002). Furthermore there is evidence of HFO under detection, especially in higher frequency bands when using macroelectrodes (as in our cases), i.e. in the FR range, which results in a lower mean frequency of detected HFO (Worrell et al., 2008).

According to previously published data, which is further corroborated by our study, the FR and R rate are significantly higher in the SOZ than in nonSOZ/nonIZ regions (Urrestarazu et al., 2007; Jacobs et al., 2008, 2009; Andrade-Valença et al., 2012). Interestingly, in patients with favorable outcomes, a prominent (though not significant) difference between rates of FR and R in the SOZ and the IZ can be observed, which might represent a more focal generator (epileptogenic tissue) of these pathological HFO; this difference was less seen in other patients. As in a study by Jacobs et al. (2008), the distinction between pathological and normal areas was worse for R than for FR. Nevertheless, the explanation for the high rates of R and FR in nonSOZ/nonIZ regions is unclear. It cannot be definitely demonstrated whether all of these marked events were actually pathological, physiological, or the propagation of pathological HFO arising from elsewhere, as was mentioned above. Spontaneous HFO of a physiological nature are difficult to distinguish from epileptogenic ones, particularly during wakefulness (Jacobs et al., 2008; Curio, 2000) since the frequency and amplitude measures alone cannot be used for this purpose (Engel et al., 2009; Nagasawa et al., 2012; Matsumoto et al., 2013). Finally, the overlap (in both amplitude and duration) between the pathological and physiological ripples is extensive (Alkawadri et al., 2014).

The main reason for focusing on the IZ is evidence of HFO linking with interictal epileptiform discharges in both mesiotemporal and neocortical epilepsy (Urrestarazu et al., 2007; Jacobs et al., 2008; Wang et al., 2013). The vast majority of interictal HFO (up to 73% of R and 92% of FR) is associated with interictal spikes or sharp waves (Urrestarazu et al., 2007; Jacobs et al., 2008). A comparison of HFO associated with interictal epileptiform discharges and unassociated HFO revealed no differences in terms of the duration (Urrestarazu et al., 2007), or the associated HFO had longer durations than the unassociated HFO with spikes (Jacobs et al., 2008). Wang and colleagues (2013) showed HFO detected in the SOZ area were of shorter duration than those not correlated to the SOZ area. As in the study by Wang et al. (2013), our data suggest longer durations of both R and FR in the IZ or nonSOZ/nonIZ than in the SOZ. These findings might be also a consequence of analyzing awake recordings with less expressed interictal discharges, and so more HFO detected this phenomenon and with shorter duration. This finding might be also explained by the work of Nagasawa (2012), who revealed that the duration of spontaneous HFO in the ripple range (namely from the occipital cortex) of a physiological nature were significantly longer than that of epileptogenic ripple HFO. Similar results were presented by Alkawadri et al. (2014). These observations are still consistent with the hypothesis that longer durations of HFO may represent longer excitatory neural processing (Niessing et al., 2005; Nishida et al., 2008; Koch et al., 2009; Manning et al., 2009; Nagasawa et al., 2012). In other studies, however, the duration of pathological (in the SOZ) and physiological (nonSOZ region) FR was not diverse (Nagasawa et al., 2012; Alkawadri et al., 2014), or the longer duration of both R (Brázdil et al., 2015) and FR was revealed within the SOZ (Jacobs et al., 2008; Matsumoto et al., 2013). The discrepancies among studies in the duration of R and FR in various regions might be explained by different proportions of included focal epilepsies (hippocampus vs. neocortex).

There have been noteworthy results regarding relative HFO amplitude in epileptic and non-epileptic regions in particular subgroups of patients. Interestingly, in the group of patients with favorable outcomes, the relative HFO amplitude (especially FR) was higher in the SOZ than in other regions; in other patients with "poor outcomes", the results of FR analysis were reversed. These results for both R and FR might contribute to neurosurgical resection planning, showing possible worse prognosis in patients with higher amplitudes especially of FR outside the SOZ. This indicates that it is possible that the true SOZ was not adequately detected. Another reason may be a more dispersed or multifocal epileptogenic zone/SOZ, a pattern which is too diffuse to permit a successful resective strategy, and so usually results in VNS implantation. Yet another reason for poor outcome may be that the result of the epileptogenic zone may include the actual epileptogenic zone (generating seizures before surgery) as well as a potential epileptogenic zone which is an area of the cortex that may generate seizures after the presurgical SOZ has been resected (Rosenow and Lüders, 2001). Seizures originating from areas not covered by electrodes but propagating to the actual electrode positions might lead to misinterpretation (Zijlmans et al., 2012).

HFO are more stable and more expressed, and the likelihood for artifact contamination is lower, during sleep. However, a review of recently presented data indicates that the effect of sleep on HFO expression differs among regions (Dümpelmann et al., 2015) and so this phenomenon might influence the observation. Some patients also experience postoperative nausea and general discomfort so they rarely reach deep stages of sleep. The differences in HFO rates between the SOZ and other remote areas were disclosed in wakefulness periods as significant (Bagshaw et al., 2009). Based on this data we decided to analyze awake recordings.

Our findings emphasize the importance of the careful interpretation of HFO, especially in cases with extensive spatial sampling or when there is an overlap between the epileptic and physiologic areas (Alkawadri et al., 2014). Based on our data, it is useful to include both ripples and fast ripples in the evaluation of the potential epileptogenic region (Zijlmans et al., 2012). Currently, there are no established criteria for distinguishing physiological from pathological HFO and SOZ areas (Engel et al., 2009; Jacobs et al.,

2016). Nevertheless, it seems that FR generated in the SOZ are more frequent, shorter, and have higher relative amplitudes than in other regions. There is, however, no clear cut-off value for these characteristics which can separate the SOZ, the IZ, and other regions.

5. Conclusion

HFO parameters (rate, amplitude, and duration) differ in epileptic and non-epileptic regions. We suggest that amplitude and duration may be as important as frequency band and rate of HFO in marking the seizure onset region or epileptogenic area and may provide additional information on epileptogenicity. To conclude, FR are more frequent, shorter, and have higher relative amplitudes in the SOZ area than in other regions. The study suggests a possible worse prognosis in patients with higher amplitudes of FR outside the SOZ.

Acknowledgments

The study was supported by the "CEITEC – Central European Institute of Technology" project (CZ.1.05/1.1.00/02.0068) from the European Regional Development Fund and by MŠMT ČR Research Program no. MSM0021622404. The technical part of the study was supported by the GACR project P103/11/0933 and the Application Laboratories of Advanced Microtechnologies and Nanotechnologies (CZ.1.05/2.1.00/01.0017), co-funded by the Operational Programme "Research and Development for Innovations", the European Regional Development Fund, and the state budget.

Supported by European Regional Development Fund - Project FNUSA-ICRC (No. CZ.1.05/1.1.00/02.0123) and Ministry of Education, Youth and Sports of the Czech Republic project no. LH15047 (KONTAKT II).

Conflict of interest: None of the authors has any conflict of interest to disclose.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.clinph.2016.10.011.

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Annex 5: Dolezalova I, Brazdil M, Rektro I, Tyrlikova I, Kuba R. Syncope with atypical trunk convulsions in a patient with malignant arrhythmia. Epileptic Disorders. 2013;15(2):171-174.

Epileptic Disord 2013; 15 (2): 171-4

Syncope with atypical trunk convulsions in a patient with malignant arrhythmia

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Received October 9, 2012; Accepted February 17, 2013

ABSTRACT – Syncope is a condition often misdiagnosed as epilepsy. Syncope caused by cardiac disturbance is a life-threatening condition and accurate diagnosis is crucial for patient outcome. We present a case study of a 71-year-old woman who was referred to our epilepsy centre with a diagnosis of refractory epilepsy. We diagnosed convulsive syncope caused by malignant cardiac arrhythmia based on the presence of cardiac asystole lasting for 20-30 seconds, which was caused by sick sinus syndrome combined with third-degree atrioventricular block. The most prominent feature of this syncope was atypical trunk (abdominal or thoracoabdominal) convulsions, which were accompanied by other motor signs (head and eye deviation and brief jerks of the extremities). In the periods between attacks, all investigations, including standard 12-lead ECG and 24-hour ECG monitoring, were normal. This case study highlights the challenge in differential diagnosis of sudden loss of consciousness. [*Published with video sequences*]

Key words: syncope, epilepsy, arrhythmia, asystole, trunk convulsion, sick sinus syndrome, central pattern generators

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doi:10.1684/epd.2013.0564

The misdiagnosis of epilepsy is a relatively common occurrence. Of patients diagnosed with epilepsy who were referred to epilepsy centres, 20-30% were found to be misdiagnosed (Benbadis, 2009). The most common conditions misdiagnosed as epilepsy were psychogenic non-epileptic attacks, followed by syncope (Benbadis, 2009). Five basic mechanisms to describe the genesis of syncope have been described: syncope may be neurally mediated, sometimes referred to as a reflex (vasovagal syncope, carotid sinus syncope, and situation syncope), caused by orthostatic hypotension, cardiac arrhythmias, structural cardiac or pulmonary disease, or mediated by the central nervous system (ictal bradycardic syncope) (Crompton and Berkovic, 2009). Cardiac arrhythmias, in particular, can cause life-threatening events.

We present a case study of a patient who was referred to our epilepsy

centre with a diagnosis of intractable epilepsy and later diagnosed with syncope and atypical trunk convulsions induced by malignant arrhythmia.

Case study

We present the case of a 71-year-old female who was treated for coronary artery disease, arterial hypertension, and type 2 *diabetes mellitus*. Her family and social history were insignificant. The first episode of unconsciousness occurred at the age of 70 without any triggering factors. Witnesses reported a sudden loss of consciousness, accompanied by brief jerks of the extremities and contractions of the abdominal wall. The patient was admitted to a local hospital, where physical examination and other investigations (basic laboratory examination, 12-lead ECG, 24-hour ECG monitoring, EEG, and brain CT) were performed. The laboratory examination and ECG monitoring were described to be normal. On EEG, there was a greater representation of theta waves in both temporal regions, but this was interpreted to be normal based on the age of the patient. Based on CT, there was only mild cortical atrophy with moderate ischaemic/degenerative changes of white matter. The frequency of seizures was approximately one seizure per month. After the second attack, antiepileptic medication with lamotrigine (LTG) was started, but was ineffective. Carbamazepine (CBZ) and levetiracetam (LEV) were then introduced without any significant influence on seizure frequency.

One year later, the frequency of seizures suddenly increased and started to appear daily. For this reason, the patient was hospitalised in a local hospital and then referred to our epilepsy centre with a diagnosis of intractable epilepsy. She was admitted to our video-EEG unit in the late afternoon for urgent care and during the first night, three habitual paroxysmal events were recorded. For video-EEG monitoring, standard scalp electrode positions (10-20 system), one-channel ECG, and simultaneous video recordings were performed.

The attacks always started with heart asystole, followed by diffuse slowing-down and attenuation of EEG, accompanied by muscle and movement artefacts (*figure 1*). Within approximately 10 seconds, the patient lost consciousness. Head and eye deviation appeared, followed by brief jerks of the upper and lower extremities, and subsequently distinct abdominal or thoracoabdominal convulsions developed. These convulsions lasted for 3-5 seconds. After spontaneous restitution of heart activity, the patient almost immediately regained consciousness without any signs of confusion, but nausea and occasional vomiting were present at the end (*video sequence 1*). We recorded one seizure in which only abdominal/thoracoabdominal contractions were present (*video sequence 2*). The duration of asystole ranged from 20 to 30 seconds. The patient was immediately admitted to our cardiology department. Based on the 12-channel ECG results, she was diagnosed with sick sinus syndrome, probably combined with third-degree atrioventricular block, and was urgently implanted with a Biotronic Talos DR pacemaker. After discharge from the hospital, the antiepileptic medication was withdrawn. The patient has now been free of syncopal attacks without any antiepileptic drugs for almost two years.

Discussion

This case study highlights the challenge in differential diagnosis of a loss of consciousness. An incorrect diagnosis may have severe consequences; the patient may not be treated appropriately, moreover, some antiepileptic drugs can be potentially

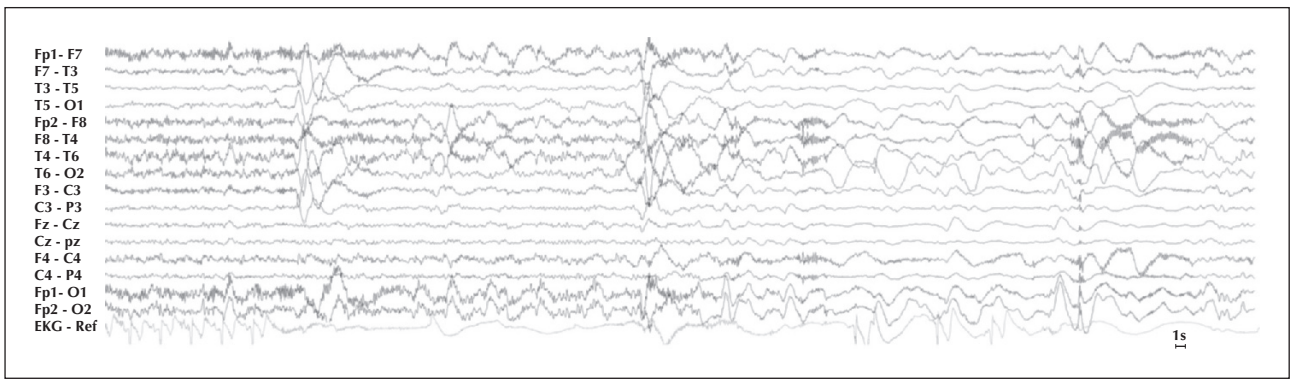

Figure 1. EEG during heart asystole.
The heart asystole is followed by the deceleration and subsequent attenuation of background activity. The EEG is contaminated with muscular artefacts.

harmful to patients with cardiac disease. The use of sodium channel blockers (for example, phenytoin and carbamazepine) in patients with cardiac-related syncope may worsen undetected heart disease through their negative chronotropic and dromotropic effects (Kenneback *et al*., 1991).

The percentage of syncopes with motor manifestations is reported to vary; some convulsions were reported in 12% of blood donors who experienced vasovagal syncope, compared with 45% of patients with malignant ventricular arrhythmias and implanted defibrillators (Lin *et al*., 1982; Aminoff *et al*., 1988). In a study by Lempert *et al*. (1994), almost 90% of healthy volunteers, in whom syncope was provoked artificially by hyperventilation, squatting, and Valsalva manoeuvre, presented with syncope with some type of convulsion. However, we presume that this is an over-representation, influenced by the study design.

The pattern of movement usually consists of multifocal arrhythmic jerks of the extremities, generalised myoclonus, and some additional movements such as head turns, oral automatisms, and righting movements (Crompton and Berkovic, 2009). In our patient, the most prominent motor characteristics were atypical trunk convulsions (we were unable to distinguish reliably between abdominal and thoracoabdominal contractions based on video recordings), a syncopal feature which has probably not been previously reported. Other similar reports include those of Ambrosetto *et al*. (2009) and Gasparini *et al*. (2011) who reported case studies of syncope with bipedal activity and gestural automatisms. The underlying pathological mechanism is believed to be the release, most likely disinhibition, of central pattern generators by anoxic cortical inactivation. Central pattern generators located at the subcortical level (mainly the brainstem and spinal cord) are responsible for rhythmic behaviour and are "normally" under neocortical control (Tassinari *et al*., 2009).

In the literature, the characteristics of patient history and description of attacks, which enable physicians to differentiate between syncope and epileptic seizures, as well as identify different aetiologies of syncope, are summarised (Sheldon *et al*., 2002; Crompton and Berkovic, 2009). We would like to point out that history or physical signs of cardiac disease should lead to a high suspicion of cardiac aetiology (Alboni *et al*., 2001). In our patient, a history of coronary artery disease was known.

It is important to stress that establishing a correct diagnosis can be complicated by the possible coexistence of syncope and seizure within one attack (Crompton and Berkovic, 2009). Attacks in which an initial syncopal event triggers an epileptic seizure are rare and occur mainly in children (Horrocks *et al*., 2005). Conversely, focal-onset seizures can cause bradycardia-induced syncope as a result of the disruption of cardiac autonomic neural discharges (Crompton and Berkovic, 2009).

This case study is an illustrative example of the importance of differential diagnosis in patients with loss of consciousness. The differential diagnosis is crucial mainly in cases with atypical course progression or clinical manifestation and in elderly patients with somatic comorbidities. In our patient, establishing a correct diagnosis and the subsequent implantation of a cardiac pacemaker were probably lifesaving. □

Acknowledgments and disclosures.

We thank Anne Johnson for grammatical assistance in writing the manuscript. This work was supported by the CEITEC-Central European Institute of Technology project (CZ.1.05/1.1.00/02.0068) from the European Regional Development Fund.

None of the authors has any conflict of interests to disclose.

Legends for videosequences

Video sequence 1

00:00 development of asystole
00:10 head and eye deviation to the left, followed by brief myoclonus of right-sided extremities
00:14 trunk convulsions
00:24 heart rate reappears spontaneously
00:29 patient regains consciousness and is oriented

Video sequence 2

00:00 development of asystole
00:10 trunk convulsions
00:20 heart rate reappears spontaneously
00:23 patient regains consciousness and is oriented

Key words for video research on *www.epilepticdisorders.com*

Syndrome: non epileptic paroxysmal disorder
Etiology: syncope (cardiac)
Phenomenology:
head deviation;
motor seizure (complex);
nonepileptic paroxysmal event
Localization: not applicable

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Annex 6: Dolezalova I, Brazdil M, Kahane P. Temporal lobe epilepsy? Things are not always what they seem. Epileptic Disorders. 2017;19(1):59-66.

Electroclinical reasoning report

Epileptic Disord 2017; 19 (1): 59-66

Temporal lobe epilepsy? Things are not always what they seem

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Received August 21, 2016; Accepted December 29, 2016

ABSTRACT – Temporal lobe epilepsy is the most frequent form of drug-resistant epilepsy referred to epilepsy surgery centres. The vast majority of lesional cases can be operated on without invasive investigation which is often not the case for non-lesional cases. Invasive investigation in non-lesional cases, however, may lead to unexpected results, as illustrated in the following case report. [*Published with video sequence on www.epilepticdisorders.com*]

Key words: temporal lobe epilepsy, invasive EEG, pseudotemporal epilepsy, posterior cingulate

Clinical data

A 33-year-old left-handed female patient started to have seizures at the age of 14. She was born from a normal uncomplicated pregnancy, and was treated for asthma in childhood. Familial history was irrelevant with the exception of a paternal cousin who suffered from moderate intellectual disability associated with epilepsy. The patient had a secondary school education and was working episodically as a civil servant. Her neurological examination was normal, except for a discrete right inferior facial palsy.

The first episode was described as an abrupt loss of contact accompanied by abnormal verbal behaviour (she repeated the same questions several times), followed by headache. A diagnosis of epilepsy was established and the patient was subsequently treated with valproic acid, which failed to control the seizures. The seizures persisted on a weekly to monthly basis despite different AEDs used in monotherapy or in combination (carbamazepine, clobazam, lamotrigine, and levetiracetam). Aura was described as an epigastric constriction, sometimes associated with gustatory hallucinations. A seizure was observed by her neurologist who described a behavioural change (the patient seemed "confused"), a preserved ability to denominate objects, right-handed nose rubbing, and amnesia (with no recollection of denominating objects).

VIDEO ONLINE

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doi:10.1684/epd.2017.0897

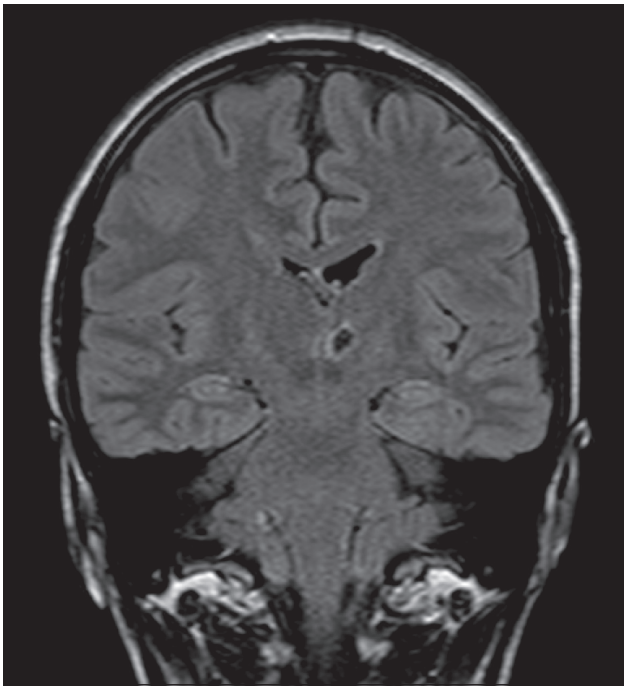

Figure 1. Preoperative MRI showing a left-sided thalamic infarction. Hippocampal sclerosis or other possible epileptogenic lesions were not identified.

EEG showed infrequent right fronto-temporal sharp waves and left frontal spikes during drowsiness. MRI showed the cavity of a left thalamic infarct, without any other abnormalities (*figure 1*).

Comments

The overall clinical presentation appears to be similar to that of temporal lobe epilepsy (TLE), which can be considered "cryptogenic" despite the presence of a left thalamic infarct. The inconsistent gustatory aura, however, could suggest an early perisylvian involvement during the seizures (Hausser-Hauw and Bancaud, 1987). The neurological examination (right inferior facial palsy) indicates the involvement of the left hemisphere (Robillard *et al*., 1983), while ictal semiology (right-handed nose rubbing) could suggest right hemispheric involvement (Catenoix *et al*., 2004). Preservation of speech suggests the involvement of the non-dominant hemisphere for language (Gillig *et al*., 1988).

Non-invasive investigations

During video-EEG monitoring, seizures were characterized by an unpleasant epigastric constriction, inconsistent preservation of speech, loss of contact, a change in facial expression, oroalimentary automatisms (mastication), upper limb automatisms (mainly left), and nose wiping or face rubbing (without clear lateralization) (*video sequence 1*). Seizures lasted approximately one minute and the patient sometimes remained confused during the postictal state, without language deficit.

Interictal EEG activity mainly showed, during sleep, interictal epileptiform discharges (IEDs) over the left fronto-temporal region (phase reversal at Fb1, T3; *figure 2A*) and, much less frequently, over the right frontal region (phase reversal at F4; *figure 2B*) or the left frontal region (phase reversal at F3; *figure 2C*). Seizures slightly differed in their EEG pattern, but typically indicated seizure onset over the left anterior temporal lobe, with secondary left hemispheric involvement and contralateral spread (*figure 3*).

Neuropsychological examination showed visual and verbal encoding difficulties; executive functions and attention were described as normal. Functional MRI supported bilateral speech representation. 18-FDG-PET showed bitemporal, but left-predominant, hypometabolism (*figure 4*).

Comments

Based on interictal EEG abnormalities, neuropsychological findings, and PET results, the patient could appear to have bitemporal epilepsy. However, ictal EEG consistently indicated the left hemisphere at seizure onset, and seizures systematically propagated over the contralateral hemisphere, which could explain bilateral dysfunctions.

The association of left-sided TLE with seizures arising from the dominant hemisphere and preserved ictal speech would be rare. In these cases, an extratemporal lobe seizure origin with temporal propagation of ictal activity seems to be more probable (Kaiboriboon *et al*., 2006). However, the structural or functional damage of a dominant hemisphere by epileptic activity can cause neuronal reorganization and redistribution of "critical" functions, as has been reported for speech and handedness which were shown to shift to the other hemisphere (Orsini and Satz, 1986; Adcock *et al*., 2003). This could be supported by left-handedness and bilateral speech representation on functional MRI. However, the distribution of IEDs over both frontal regions raised a red flag which forced us to also consider extra-TLE with propagation of ictal activity to the temporal region.

Invasive EEG (iEEG) was considered as mandatory to answer the following question: does this patient have TLE, temporal "plus" epilepsy (Barba *et al*., 2007), or extra-TLE?

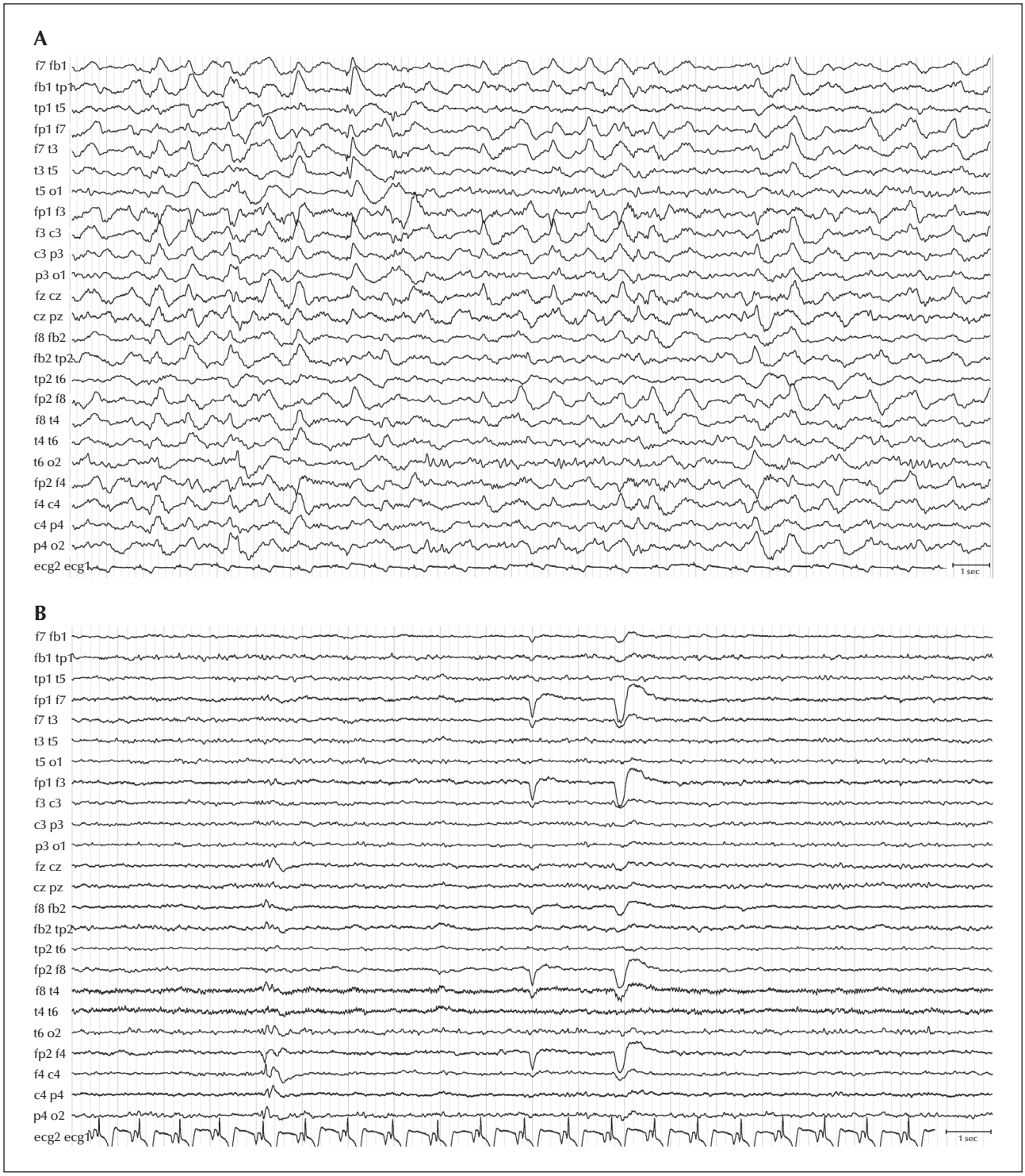

Figure 2. Distribution of interictal epileptiform discharges (IEDs) on scalp EEG. (A) The majority of IEDs were present in the left-sided fronto-temporal area (phase reversal at electrodes Fb1, T3). (B) There were also less frequent IEDs over the right-sided frontal area (phase reversal at electrodes F4).

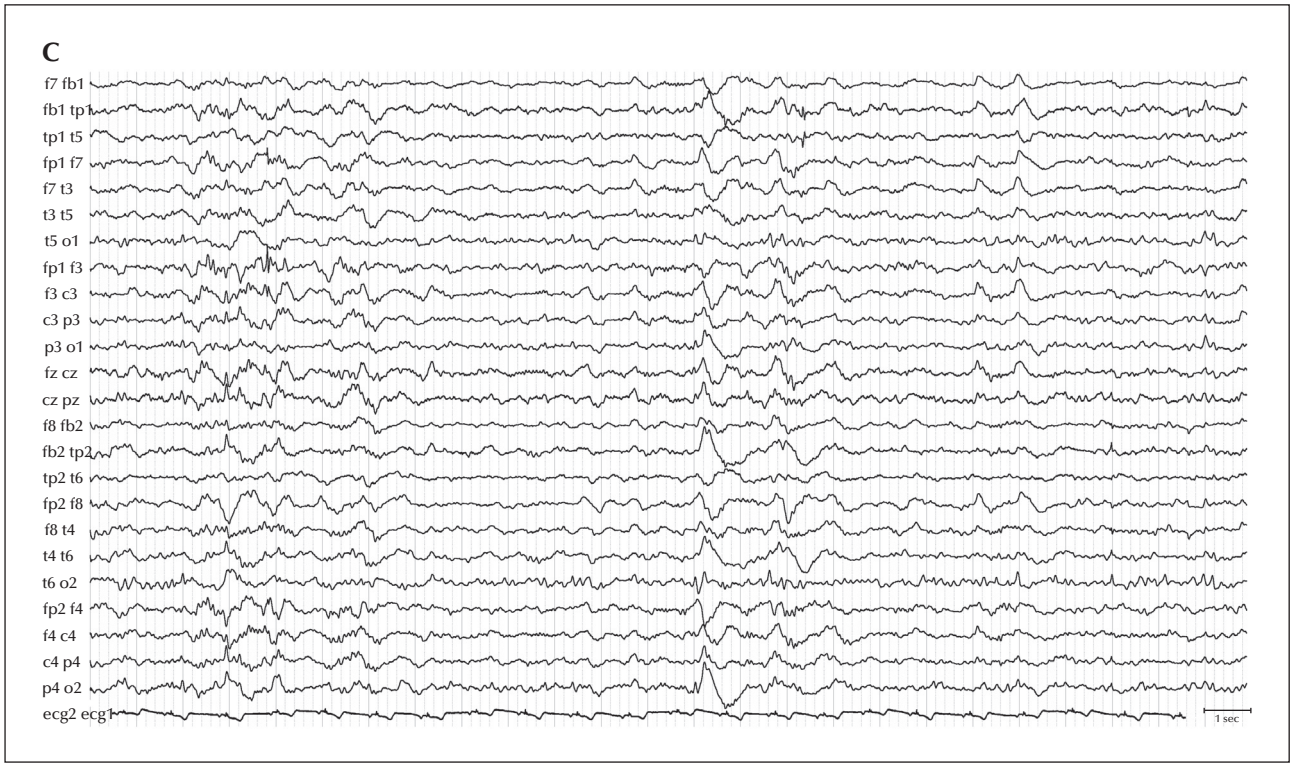

Figure 2. (*Continued*). (C) Rarely, IEDs could be found over the left frontal regions (phase reversal at electrode F3).

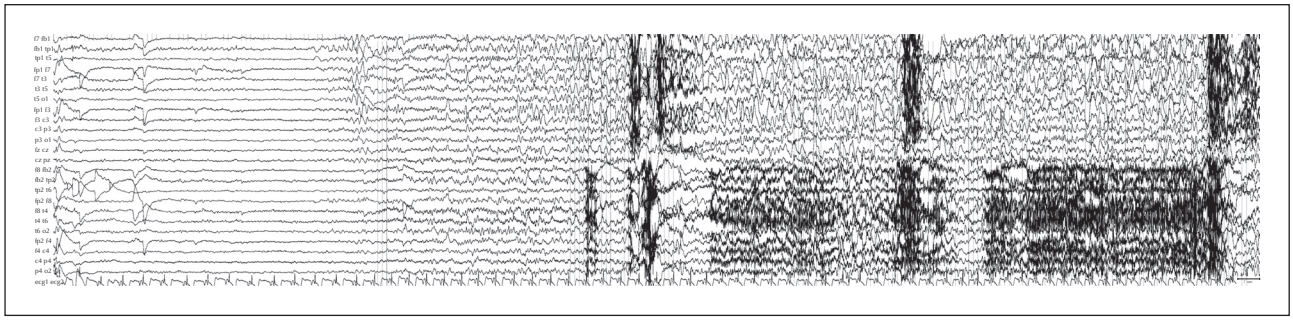

Figure 3. Ictal scalp EEG showing the typical pattern for the patient. The seizures started with a short flattening over the left anterior temporal lobe, followed by irregular theta waves in the same area. After, clear-cut rhythmic activity appeared; this rhythmic activity started on the left side, but rapidly spread over the right hemisphere. The left-sided ictal activity predominated throughout the entire seizure.

Invasive investigation

A large temporo-perisylvian stereoelectroencephalography (sEEG) study was performed that targeted the mesial and lateral temporal lobe structures, as well as the extra-temporal lobe regions that can trigger temporal lobe symptoms (*e.g.* the orbito-frontal cortex, insular cortex, and posterior cingulate cortex) (*figure 5*).

IEDs either involved mesiotemporal structures or, independently, the posterior cingulate region (*figure 6A*) . All seizures, however, started within the posterior cingulate before becoming symptomatic when they involved the mesiotemporal lobe structures (*figure 6B and 7*).

Comments

This patient is a typical example of what has been described as pseudo-temporal epilepsy, in which seizures start in extra-temporal lobe structures and later spread over the temporal lobe region, therefore

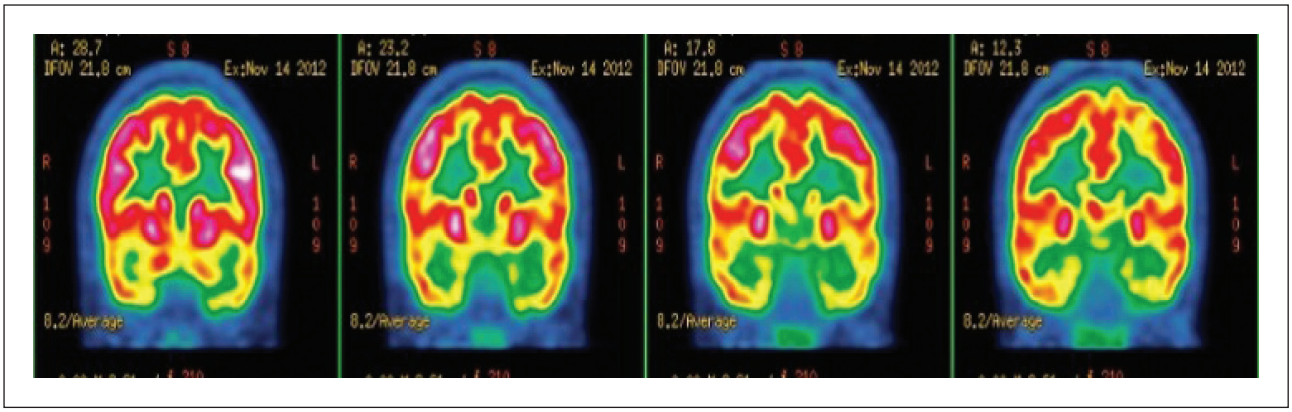

Figure 4. Preoperative positron emission tomography (PET) showing bilateral temporal hypometabolism, which was slightly more pronounced on the left side.

mimicking temporal semiology (Andermann, 2003). Extra-temporal lobe regions include the orbito-frontal cortex (Shihabuddin *et al*., 2001), the insula (Isnard *et al*., 2000), and the parieto-occipital regions (Williamson *et al*., 1992; Palmini *et al*., 1993; Liava *et al*., 2014; Francione *et al*., 2015), especially the posterior cingulate (Devinsky *et al*., 1995; Alkawadri *et al*., 2013; Enatsu *et al*., 2014). Alkawadri *et al*. (2013) reported a group of 14 patients with cingulate epilepsy; within this group there were also four patients with posterior cingulate epilepsy and their seizures resembled temporal lobe seizures in all patients (Alkawadri *et al*., 2013). Enatsu *et al*. (2014) analysed a case series of seven patients with posterior cingulate epilepsy, four of whom exhibited temporal lobe seizures and the rest had motor seizures (including bilateral tonic seizures and hypermotor seizures).

The differential diagnosis between temporal and pseudo-temporal epilepsy remains a diagnostic challenge, especially in non-lesional cases. The distribution of IEDs can be very helpful in terms of searching for a solution. IEDs in TLE often remain limited to the temporal lobe region; in other types of epilepsies they spread over different regions (Remi *et al*., 2011). However, IEDs in posterior cingulate epilepsy have a large tendency to propagate into the temporal region, as was demonstrated by Alkawadri *et al*. (2013). These authors reported "typical" temporal IEDs in three out of four patients (in two patients over anterior temporal areas and in one patient over posterior temporal areas); in contrast, frontal IEDs were found only in one patient (Alkawadri *et al*., 2013). Also, Elwan *et al*. (2013) did not find any statistical significant differences between temporal and pseudo-TLE when analysing the distribution of IEDs and seizure-onset pattern on scalp EEG (Elwan *et al*., 2013). To sum up, IEDs often also propagate over temporal areas in extra-temporal epilepsies. However, the presence of IEDs over extra-temporal areas is very often associated with an extra-temporal seizure origin despite typical temporal seizure semiology.

Action taken

Three surgical strategies could be considered:
– perform a standard temporal lobe resection, *i.e*. a resection of the symptomatogenic zone; this

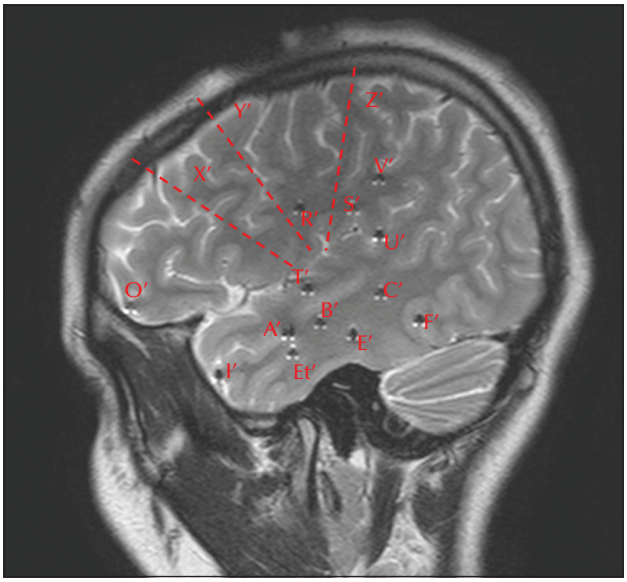

Figure 5. Electrode positions for invasive EEG monitoring. The positions of electrodes in the left temporal lobe are the following: A′: amygdala; B′: anterior hippocampus; C′: posterior hippocampus; I′: temporal pole; Et′: entorhinal cortex; T′, U′: temporal operculum; E′, F′: temporobasal region. The positions of electrodes in the left extra-temporal lobe structures are the following: O′: fronto-orbital cortex; R′: frontal operculum; S′: parietal operculum; V′: cingulum (posterior part); X′: anterior insula (dotted line); Y′: posterior insula (dotted line); Z′ (dotted line).

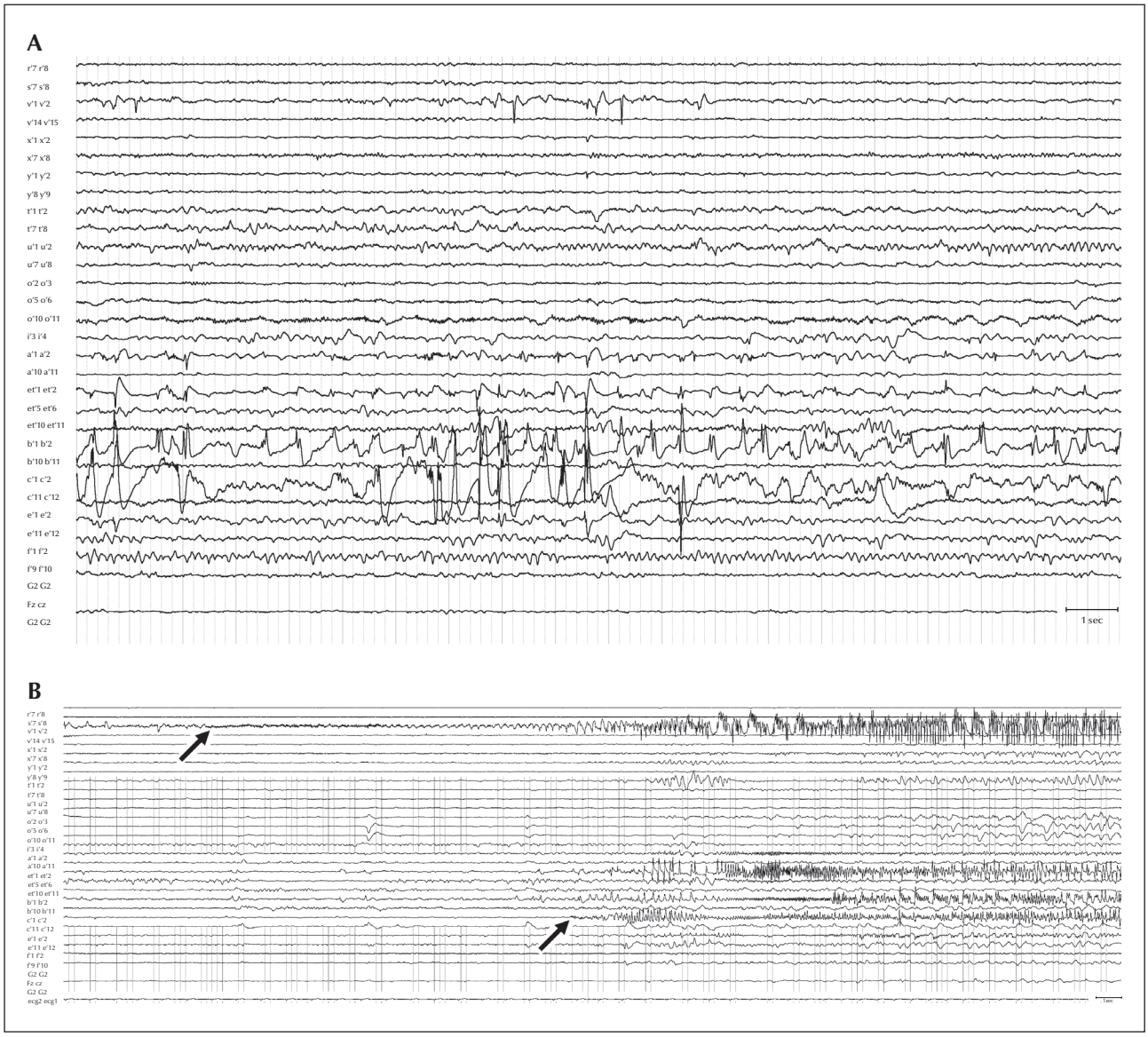

Figure 6. The results of invasive EEG. (A) Distribution of interictal epileptiform discharges (IEDs) on invasive EEG. IEDs dominated in the area of left-sided mesiotemporal structures (left amygdala: electrode Aĭ1-2; left entorhinal cortex: electrode Etĭ1-2; and left hippocampus: electrodes Bĭ1-2 and Cĭ1-2), but there were also IEDs and bursts of rapid activity (blue arrow) in the area of the left posterior cingulum (electrode Vĭ1-2). (B) Ictal findings on invasive EEG. The seizures started with low-voltage fast (LVF) activity in the left side of the posterior cingulum (first arrow); LVF activity propagated to the left-sided mesiotemporal structures, where the symptomatogenic zone was localized (second arrow).

strategy should be considered as only palliative and could postoperatively aggravate the memory deficit;

– perform a new iEEG study in order to better delineate the amount of the mesial parietal cortex that should be resected; this is a possible option, although the benefit/risk ratio cannot be clearly evaluated;

– perform a very focal resection of the posterior cingulate cortex surrounding the cingulate electrode.

The latter strategy was finally chosen, as the shape and signal of that part of the posterior cingulate retrospectively appeared "abnormal" (*figure 8*). The histopathological specimen, however, proved negative. Another possibility would be to perform thermocoagulation in the area of the posterior cingulum. The effectiveness of this procedure is not very high; only 7% of patients remain seizure-free one year after surgery (Bourdillon *et al.*, 2016).

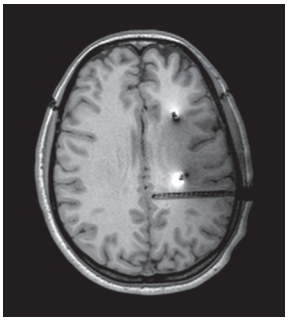

Figure 7. More detailed view of the position of electrode Vĩ. The low-voltage fast activity started in the mesial contacts of this electrode, encompassing the left side of the posterior cingulum, as seen in this image.

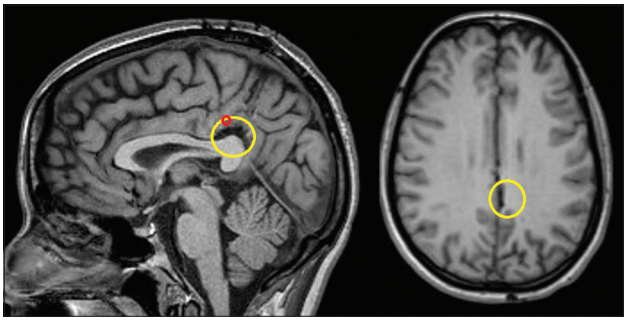

Figure 8. The second preoperative MRI. We retrospectively identified a discrete change on MRI (yellow circle). The position of seizure onsets is marked by red dots.

Follow-up

The patient is completely seizure-free three years after surgery (Class 1; according to International League Against Epilepsy Classification [Wieser *et al*., 2001]). AEDs have been substantially reduced and at present, the patient is only being given 800 mg of carbamazepine. Interictal EEG shows infrequent right temporal sharp waves.

Conclusion

This case report illustrates that atypical presentation of non-lesional TLE epilepsy must be referred for iEEG evaluation. Invasive evaluation must be designed to allow a distinction between mesial and neocortical temporal lobe onset, as well as consideration for possible extra-temporal onset, as in the present case. □

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

Disclosures.
None of the authors have any conflict of interest to declare.

Legend for video sequence

A typical patient seizure. The seizure semiology appears late (approximately 30 seconds from the first change in EEG). In this first seizure, limb automatisms of the right arm are observed and speech is preserved during the seizure. In the postictal state, the patient was amnesic for the seizure.

Key words for video research on www.epilepticdisorders.com

Phenomenology: aura (abdominal), automatisms
Localisation: cingulate gyrus, temporal (left)
Epilepsy syndrome: focal non-idiopathic parietal
Aetiology: not applicable

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TEST YOURSELF

(1) In pseudotemporal epilepsy,
A. do seizures always spread to mesio-temporal lobe structures?
B. is seizure onset localized to the extra-temporal lobe structures?
C. is the seizure semiology similar to that of temporal lobe seizures?
D. is an extra-temporal lobe lesion always present on MRI?

(2) Which type of extra-temporal epilepsy can manifest as pseudotemporal epilepsy (more than one answer may be correct)?
A. Occipital
B. Parietal
C. Frontal
D. Insular

(3) Which of the following examinations is the most relevant in the diagnosis of non-lesional pseudo-temporal epilepsy?
A. Video-EEG monitoring
B. 18-FDG PET
C. Neuropsychological evaluation
D. Invasive EEG

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".

Annex 7: Dolezalova I, Schachter S, Chrastina J, Hemza J, Hermanova M, Rektor I, Pazourkova M, Brazdil M. Atypical handedness in mesial temporal lobe epilepsy. Epilepsy & Behavior. 2017;72:78-81.

Epilepsy & Behavior 72 (2017) 78–81

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Atypical handedness in mesial temporal lobe epilepsy

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ARTICLE INFO

Article history:
Received 6 November 2016
Revised 2 January 2017
Accepted 26 January 2017
Available online 7 June 2017

Keywords:
Mesial temporal lobe epilepsy
Handedness
Left-handed
Right-handed
Age at epilepsy onset
Atypical dominance

ABSTRACT

Objective: The main aim of our study was to investigate the handedness of patients with mesial temporal lobe epilepsy (MTLE). We also sought to identify clinical variables that correlated with left-handedness in this population.
Methods: Handedness (laterality quotient) was assessed in 73 consecutive patients with MTLE associated with unilateral hippocampal sclerosis (HS) using the Edinburgh Handedness Inventory. Associations between right- and left-handedness and clinical variables were investigated.
Results: We found that 54 (74.0%) patients were right-handed, and 19 (26%) patients were left-handed. There were 15 (36.6%) left-handed patients with left-sided seizure onset compared to 4 (12.5%) left-handed patients with right-sided seizure onset ($p = 0.030$). Among patients with left-sided MTLE, age at epilepsy onset was significantly correlated with handedness (8 years of age [median; min-max 0.5–17] in left-handers versus 15 years of age [median; min-max 3–30] in right-handers ($p < 0.001$).
Conclusions: Left-sided MTLE is associated with atypical handedness, especially when seizure onset occurs during an active period of brain development, suggesting a bi-hemispheric neuroplastic process for establishing motor dominance in patients with early-onset left-sided MTLE.

1. Introduction

The left and right hemispheres differ in their functional organization and specialization. The left hemisphere is typically responsible for processes involved in language and verbal memory. Left-sided language dominance is present in nearly all right-handers as well as the majority of left-handers. Damage to the left hemisphere in utero or during early childhood is often associated with network reorganization, resulting in atypical lateralization of hemispheric functions such as language, verbal memory, and motor dominance (handedness) [1]. For example, several authors have demonstrated atypical lateralization of language and memory functions in patients with left-sided mesial temporal lobe epilepsy (L-MTLE) [2–7]. Based on this work, it appears that the crucial variable determining the likelihood of cerebral reorganization is the age at epilepsy onset; i.e., the lower the age of epilepsy onset, the greater the probability of atypical lateralization of function [6].

In addition to atypical hemispheric dominance for language and verbal memory associated with L-MTLE, there is a correlation between left-sided cerebral damage or seizure onset and atypical handedness [8–14]. For example, in 1959, Penfield and Roberts reported that 27% of 246 patients with epilepsy and focal left-sided brain injury were left-handed compared to only 8% of 276 patients with epilepsy and focal right-sided brain injury [10]. What remains unclear is the extent to which frontal lobe pathology, with or without frontal lobe seizure onset, is a pre-requisite for atypical handedness in patients with epilepsy, given the localization of motor control in the frontal lobe. In light of the growing evidence that MTLE is a brain network disease, with widespread extra-temporal anatomic and functional alterations [15], we hypothesized that MTLE would be associated with atypical handedness. We further speculated that atypical handedness would be associated with L-MTLE, reflecting the increased likelihood of atypical handedness lateralization associated with left-sided lesions, and early age of seizure onset, given the known correlation between young age and atypical hemispheric function [1,16]. The main aim of our study was therefore to assess handedness in patients with MTLE. We also sought to identify clinical variables that correlated with left-handedness in this population.

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http://dx.doi.org/10.1016/j.yebeh.2017.01.034
1525-5050/

2. Methods

We retrospectively analyzed handedness in 73 consecutive adult patients (41 females, 32 males) with drug-refractory MTLE associated with unilateral hippocampal sclerosis (HS). Handedness was assessed with the Edinburgh Handedness Inventory [17]. A laterality quotient (LQ) which ranged from −100 to 100 was calculated for each patient as described previously [17]. Patients with LQ from 100 to 0 were defined as right-handers. Patients with LQ from 0 to −100 were defined as left-handers. All patients underwent investigation for epilepsy surgery, including brain MRI, neuropsychological tests, and interictal/ictal semi-invasive video-EEG monitoring with sphenoidal electrodes, including ictal semiology analysis. Positron emission tomography (PET), interictal/ictal single photon emission tomography (SPECT), subtraction ictal SPECT co-registered to MRI (SISCOM) and invasive EEG (SEEG) were performed only in a subset of patients based on their clinical data and expert consensus. The inclusion criteria differ between surgically and medically treated patients. In medical group, only patients with unilateral temporal seizure onset and anatomically concordant HS on MRI were included. The HS was radiologically defined as unilateral hippocampal atrophy and increased signal in the hippocampus [18]. We excluded patients with suspicion of dual pathology, including bilateral HS, and bilateral seizure onset. In surgical group, we included only patients who underwent anteromesial temporal lobe resection, the presence of HS was confirmed histopathologically and was classified as having Engel 1a outcome at one year postsurgical follow-up [19]. Demographic data, including age at epilepsy onset, duration of epilepsy, performance of surgery, number of seizures per month, occurrence of generalized tonic-clonic seizures (GTCS), and type or age of initial precipitating injury were obtained by medical chart review.

The statistical analysis utilized Fisher's exact test or Mann-Whitney test according to their condition of validity. For all tests, a p value <0.05 was considered statistically significant.

All patients gave their informed consent prior to participation in the study and study approval was granted by the ethical committee at St. Anne's University Hospital.

3. Results

Among 73 enrolled patients with MTLE (46 [63%] patients underwent surgery, 27 [37%] were treated medically), HS was lateralized to the right in 32 (43.8%) patients and to the left in 41 (56.2%) patients. We did not find any statistically significant differences in demographics between patients with R-MTLE and L-MTLE (Table 1). Overall, 54 (74.0%) patients were right-handed and 19 (26%) patients were left-handed. The proportion of left-handers was statistically significantly higher in patients with L-MTLE than in patients with R-MTLE: 15 (36.6%) patients with L-MTLE were left-handed compared with 4 (12.5%) patients with R-MTLE (p = 0.030, Fig. 1).

Table 1
The comparison of demographic data between patients with right- and left-sided MTLE.

	Right-sided MTLE (n = 32)	Left-sided MTLE (n = 41)	p-Value
Age at epilepsy onset Median (min-max)	13.5 (0.5–41)	13 (0.5–30)	1.000
Duration of epilepsy Median (min-max)	15 (5–20)	15 (6–26)	1.000
Surgery Y/N n(%)	30 (93.8)/2(6.2)	38 (92.7)/3 (7.3)	1.000
Number of seizures per month ≥5 seizures/<5 seizures n(%)	26 (81.3)/6 (18.7)	34 (82.9)/17 (17.1)	1.000
GTCS Y/N n(%)	14 (43.8)/18 (56.3)	16 (39.0)/25 (61.0)	0.811
Initial precipitating injury n (%)	9 (28.1)	19 (46.3)	0.147

GTCS – generalized tonic-clonic seizures, MTLE – mesial temporal lobe epilepsy, N – no, Y – yes.

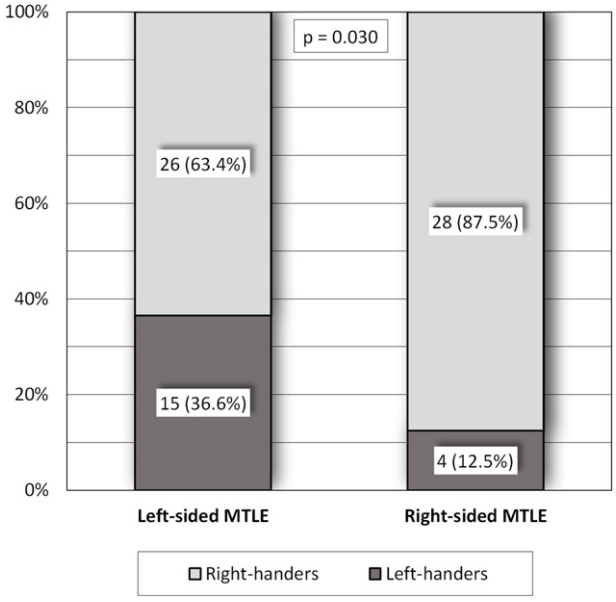

Fig. 1. Difference in left-handers representation between patients with left- and right-sided MTLE MTLE – mesial temporal lobe epilepsy.

We then assessed for clinical variables that correlated with handedness in patients with L-MTLE, and, separately, in patients with R-MTLE (Table 2). This revealed that in patients with L-MTLE MTLE, age of epilepsy onset correlated with handedness (Fig. 2). Left-handed patients with L-MTLE had an earlier age of epilepsy onset (median 8 years of age, min-max 0.5–17) compared with right-handed patients with L-MTLE (median 15 years of age, min-max 3–30; p < 0.001). No other clinical variables, including the presence of initial precipitating injury, correlated with handedness in patients with L-MTLE, and there were no clinical variables associated with handedness in the patients with R-MTLE.

Table 2
Comparison of demographic data between left- and right-handers, analysis done separately for left-sided MTLE and right-sided MTLE.

Left- sided MTLE

	Left-handers (n = 15)	Right-handers (n = 26)	p-Value
Age at epilepsy onset Median (min-max)	8 (0.5–17)	15 (3–30)	<0.001
Duration of epilepsy Median (min-max)	16 (6–26)	16 (8–25)	0.103
Surgery Y/N n(%)	13 (86.7)/2 (13.3)	25 (96.2)/1 (3.8)	0.543
Number of seizures per month ≥5 seizures/<5 seizures n(%)	11 (73.3)/4 (26.7)	23 (88.5)/3 (11.5)	0.390
GTCS Y/N n(%)	9 (34.6)/17 (65.4)	7 (46.7)/8 (53.3)	0.517
Initial precipitating injury n (%)	7 (46.6)	12 (46.2)	1.000

Right-sided MTLE

	Left-handers (n = 4)	Right-handers (n = 28)	p-Value
Age at epilepsy onset Median (min-max)	19 (1.5–30)	13.5 (0.5–41)	1.000
Duration of epilepsy Median (min-max)	15 (10–20)	14.5 (5–25)	0.129
Surgery Y/N n(%)	3 (75)/1 (25)	27 (96.4)/1 (3.6)	0.238
Number of seizures per month ≥ 5 seizures/< 5 seizures n(%)	4 (100)/0 (0)	22 (78.6)/6 (21.4)	0.566
GTCS Y/N n(%)	2 (50)/2 (50)	12 (42.9)/16 (57.1)	1.000
Initial precipitating injury n (%)	9 (32.1)	0 (0)	0.303

GTCS – generalized tonic-clonic seizures, MTLE – mesial temporal lobe epilepsy, N – no, Y – yes.

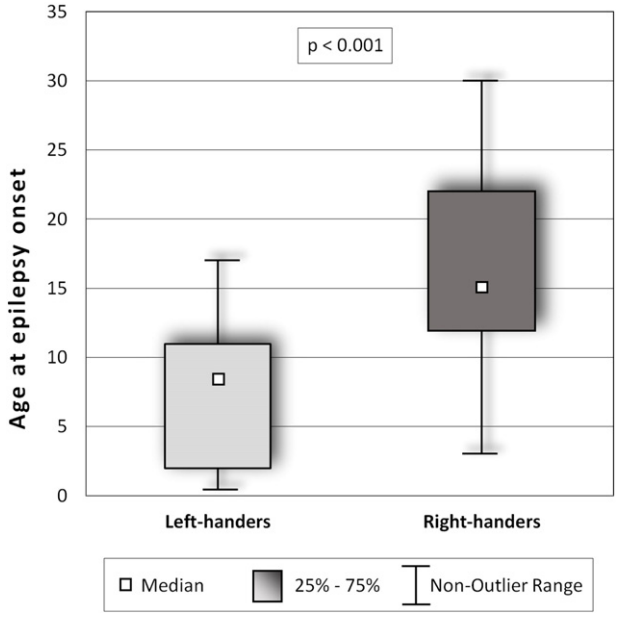

Fig. 2. Difference in age at epilepsy onset between left-handers and right-handers within the left-sided MTLE.

4. Discussion

There is compelling evidence in the literature supporting altered lateralization of language and verbal memory functions in patients with MTLE. Approximately 20–30% of patients with L-MTLE exhibit atypical (bilateral or right-sided) language dominance. In contrast, atypical language dominance is rare in patients with R-MTLE [6,7]. Similar reorganization of verbal memory lateralization has been reported. For example, Richardson et al. proved atypical activation of right hippocampus in left-sided MTLE [2]. Powell et al. confirmed these results, and moreover, demonstrated that reorganization of memory was not sufficient to support normal memory functioning [3]. An analysis of verbal memory processing (encoding and retrieval) showed different patterns of activation among healthy controls, patients with L-MTLE and patients with R-MTLE [4]. For verbal memory processes, there was greater activation of frontal, temporal, and parietal lobes in L-MTLE patients than in healthy controls.

Less information is available for handedness patterns in patients with MTLE. We published a case report of a 19-year-old female patient with drug-refractory MTLE [20] who had unequivocal shift in handedness correlated in time with epilepsy onset. We hypothesized that this handedness shift was caused by seizures. In the present study, we extend the earlier findings by showing a 3-fold elevation of left-handedness in L-MTLE compared to R-MTLE and, further, a correlation with age of epilepsy onset. The similar increase of left-handedness was present in the study of Sveller et al. (2006) who analyzed the group of 74 patients with left-sided epilepsy and 70 control subjects. There were 18% left-handers in patients' group in comparison with 4% left-handers in control group [21]. The higher incidence of atypical handedness (left-handedness and ambidexterity) in association with epilepsy was also present in study of Slezicki et al. (2009). Handedness was not associated with sex, age, seizure type, age at epilepsy onset, type or side of EEG or brain imaging abnormalities, family history of seizures, drug-resistance, or history of epilepsy surgery [22]. This study has several limitations. First, we included both operated and unoperated patients. In operated patients, the side of epileptogenic zone was confirmed by complete seizure freedom after surgery. In unoperated patients, while we required a high level of consistency in pre-surgical data, we lack definitive confirmation of the seizure focus. Second, we utilized the Laterality Quotient as originally described by Oldfield [17], though another scoring method, the Laterality Score, is more sensitive to atypical or pathological left-handedness. Third, handedness in family members was not fully evaluated in our study due to incomplete data in some patients. Finally, hand preference, especially for writing, can vary by cultural background [23]. However, all participants in our study were from the Czech or Slovak Republics, with a left-handedness rate among the general population of 10% (National Health Institute official report), similar to the proportion of left-handed patients with R-MTLE in our study (12%). This suggests that the elevated rate of left-handedness in patients with L-MTLE represents so-called "pathological" left-handedness.

Interestingly, the only clinical variable that correlated with left-handedness in patients with L-MTLE was young age at epilepsy onset. The median age at epilepsy onset was 8 years in left-handers compared with a median age of 15 years in right-handers. This suggests that the reorganization of motor dominance is age-dependent, as has also been demonstrated for language dominance [6]. Our results are further supported by other studies focusing on structural and functional brain changes associated with long-term MTLE [16,24–26]. For example, Janszky et al. showed that interictal epileptiform discharges activated brain plasticity and subsequent hemispheric reorganization for language functions from left to right [26]. We presume a similar phenomenon is responsible for reorganization of motor dominance, especially given the evidence of altered connectivity between temporal, frontal, and parietal lobes in MTLE [16], but this requires further study. In addition, it would be valuable to utilize functional MRI in this population for confirmation of hemispheric dominance and to correlate handedness with lateralization of language function and verbal memory.

In conclusion, L-MTLE is associated with atypical handedness, especially when seizure onset occurs during an active period of brain development, suggesting a bi-hemispheric neuroplastic process for establishing motor dominance in patients with early-onset left-sided MTLE.

Conflict of interest

The authors have no conflicts of interest to disclose.

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Annex 8: Kojan M, **Dolezalova I**, Koritakova E, Marecek R, Rehak Z, Hermanova M, Brazdil M, Rektor I. Predictive value of preoperative statistical parametric mapping of regional glucose metabolism in mesial temporal lobe epilepsy with hippocampal sclerosis. Epilepsy & Behavior. 2018;79:46-52.

Epilepsy & Behavior 79 (2018) 46–52

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Predictive value of preoperative statistical parametric mapping of regional glucose metabolism in mesial temporal lobe epilepsy with hippocampal sclerosis

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ARTICLE INFO

Article history:
Received 4 July 2017
Revised 9 November 2017
Accepted 11 November 2017
Available online 13 December 2017

ABSTRACT

Objective: This study was designed to use statistical parametric mapping of interictal positron-emission tomography using [$_{18}$F]Fluorodeoxyglucose (FDG-PET) to compare the brain metabolisms of patients with mesial temporal lobe epilepsy (MTLE)/hippocampal sclerosis and controls. Another aim of this study was to analyze the potential differences among patients in terms of epilepsy duration, side of hippocampal sclerosis, histopathological findings, insult in their history, and postoperative outcomes.
Methods: We analyzed FDG-PET scans from 49 patients with MTLE/hippocampal sclerosis and 24 control subjects. We analyzed the differences in regional glucose metabolism between the patients and the control group and within the patient group using multiple variables.
Results: We observed widespread hypometabolism in the patient group in comparison with the control group in temporal and extratemporal areas on the epileptogenic side (ES). On the nonepileptogenic side (NES), we observed the most hypometabolism in the thalamus and the anterior and middle cingulate gyrus. In the group of patients with more severe hippocampal sclerosis, we observed statistically significant hypometabolism in the insula on the ES. In patients with poor postoperative outcomes, we found statistically significant hypometabolism in the insula on the ES and the temporal pole (TP) on the NES. Patients with any insult in their history showed hypermetabolism in the TP on both sides.
Conclusion: Our study showed that there are widespread changes in metabolism in patients with MTLE in comparison to controls, either inside or outside the temporal lobe. There are significant differences among these patients in terms of postoperative outcomes, degree of hippocampal sclerosis, and insults in their history.

1. Introduction

The value of Positron-emission tomography (PET) using [$_{18}$F]fluorodeoxyglucose (FDG-PET) in the presurgical evaluation of patients with mesial temporal lobe epilepsy (MTLE) associated with hippocampal sclerosis (HS) [MTLE/HS] is well established [1,2]. In some earlier papers, the visual analysis of PET was found to be reliable both in lateralizing the seizure onset zone and in predicting excellent postoperative outcomes in temporal lobe epilepsy (TLE) [3,4]. However, visual analysis is associated with large variability among investigators. For that reason, methods of quantitative PET analysis have been developed. The first approach is based on glucose metabolic rate calculations in predefined regions of interest (ROIs). These values are compared with the rates from the contralateral side homologous ROI or with the normalized metabolic values from a control group. The definition of the ROI, and its size, shape, and position varies among studies, making data comparison very difficult [2]. Voxel-based approaches such as statistical parametric mapping (SPM) [5] and the asymmetry index [6] do

Abbreviations: SPM, statistical parametric mapping; ES, epileptogenic side; NES, nonepileptogenic side; FDR, false discovery rate; MTLE, mesial temporal lobe epilepsy; TLE, temporal lobe epilepsy; HS, hippocampal sclerosis; TP, temporal pole; FCD, focal cortical dysplasia; ROI, region of interest.

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https://doi.org/10.1016/j.yebeh.2017.11.014
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not depend on the selection of the ROI. The SPM method assesses the null hypothesis at each voxel with univariate statistics and constructs an image from its results. Statistical parametric mapping does not require a priori hypotheses about the location and extent of effects.

We conducted this study with interictal FDG-PET using SPM analysis in order to compare regional glucose between patients with MTLE/HS and a group of control subjects and to analyze the potential differences among patients in terms of epilepsy duration, side of HS, histopathological findings, insult in their history, and postoperative outcomes.

2. Methods

2.1. Case selection, demographics, and history data

We retrospectively reviewed all of the patients with histopathologically proven HS who underwent anterior-medial temporal lobe resection at the Brno Epilepsy Center between 2005 and 2011. The review included patients with a well-documented postoperative outcome for at least 3 years after the surgery and comprehensive results of the histopathological investigation. Patients with other pathologies including dual pathology on magnetic resonance imaging (MRI) and/or without a histopathological investigation were excluded from the study unless there was a finding of focal cortical dysplasia (FCD) of the pole of the resected temporal lobe, which was associated with HS. Clinical data included personal disease history, age at epilepsy onset, epilepsy duration, age at the time of the evaluation, and the postoperative outcome according to the International League Against Epilepsy (ILAE) classification [7].

2.2. Presurgical evaluation

The patients were epilepsy surgery candidates who underwent a comprehensive presurgical evaluation at the Brno Epilepsy Center. Magnetic resonance imaging scans were obtained using the Siemens 1.5 T MRI scanner. Video-EEG monitoring was performed on the 64-channel and 128-channel Alien Deymed systems. All patients had a neuropsychological evaluation targeting memory functions, and patients with language-dominant TLE underwent Wada testing in order to predict the postoperative memory outcome. If the noninvasive evaluations provided discordant data concerning the potential epileptogenic zone, invasive Electroencephalography (EEG) was performed. In all patients, functional neuroimaging techniques (FDG-PET) were performed; and in most patients, interictal/ictal Single-photon emission computed tomography (SPECT) were also performed. Standard anterior-medial temporal lobe resection was based on the results of a presurgical evaluation.

2.3. Histopathology

Standard histopathological examination of hippocampal and temporal pole (TP) resection specimens was performed on formalin-fixed paraffin-embedded tissues. For the grade of HS, the grading system by Wyler was used [8]. For FCD in the TP, the classification system reported by Palmini et al. [9] was used.

2.4. Patient population, surgery, outcome, and histopathology

We included 49 patients (27 female, 22 male) in the final analysis. The age of the patients at the time of the preoperative investigation ranged from 16 to 59 years with a median of 40 years. The active epilepsy duration ranged from 4 to 58 years with a median of 25 years. Of the 49 patients, 21 (42.9%) had some type of insult in their history (12 patients had encephalitis/meningoencephalitis, and 9 patients had febrile seizures). Of the 49 patients, 27 (55.1%) had left-sided (language-dominant) MTLE/HS, and 22 patients (44.9%) had right-sided (language-nondominant) MTLE/HS.

The time after surgery ranged from 2 to 7 years with a median of 4.5 years. At the last follow-up visit, according to the ILAE outcome classification [7], 31 out of 49 patients (63.3%) were classified as Outcome Group 1 (completely seizure-free since the surgery), 7 (14.3%) as Outcome Group 2 (only auras since the surgery), 6 (12.2%) as Outcome Group 3 (one to three seizure days per year), 3 (6.1%) as Outcome Group 4 (from 4 seizure days per year to 50% seizure reduction from baseline seizure days), and 2 (4.1%) as Outcome Group 5 (less than 50% seizure reduction from baseline seizure days).

Precise grading of HS (Wyler grading system) [8] was available for 34 patients. Of those 34 patients, 6 (17.6%) were classified as Wyler I/II (low-grade HS) and 28 (82.4%) as Wyler III/IV (high-grade HS). Patients classified as low-grade HS did not differ significantly from the patients classified as high-grade HS in terms of postoperative outcome (ILAE I + II in 55.5% of patients with low-grade HS and 67.6% in high-grade HS respectively; Fisher's exact test, $p = 1.0$). Histolopathological evaluations revealed FCD of type I a/b in the TP in 13 patients (26.5%) (type Ia in 8 patients and type Ib in 5 patients).

All patients signed informed consent forms. The study was approved by the local ethics committee.

2.5. Control group

For the control group, we selected 24 (13 female, 11 male) patients with FDG-PET images acquired within oncological screenings. The age of the control subjects at the time of imaging ranged from 16 to 54 years with a median of 34.5 years. The control subjects were without any findings on their MRI scans and without any neurological or psychiatric diagnoses. No disorder in the central nervous system was found, and no drugs influencing brain metabolism were taken by these control subjects. Their FDG-PET findings were assessed as normal.

2.6. FDG-PET image acquisition

[$_{18}$F]Fluorodeoxyglucose PET scans were available for SPM analysis in all 49 (27 female, 22 male) patients and in the 24 (13 female, 11 male) control subjects. Both patients and controls underwent the same procedure. Patients were imaged as outpatients in the interictal state. The PET images for both groups were acquired using a Siemens ECAT ACCEL PET scanner (three detection rings with lutetium orthosilicate type crystals and 16.2 cm axial field of view (FOV); Erlangen, Germany) in 3-D mode using the “Brain” protocol. The intrinsic spatial resolution of the scanner was 6.3 mm at full width at half maximum (FWHM) 1 cm from the center of the FOV, and 6.7 mm at FWHM 10 cm from the center of the FOV. Subjects prepared by fasting for 6 h before the scan and resting in a quiet, darkened room for 50–60 min after FDG administration. The dose of FDG administered was 200 MBq ± 15% per subject with no weight differentiation. The emission acquisition time in 3-D mode was 10 min. Forty-seven tomographic slices with a 3-mm slice thickness were reconstructed with a 128 × 128 iteration matrix with 6 iterations and 16 subsets, and a 6 mm FWHM Gaussian filter was applied.

2.7. Image preprocessing for SPM analysis

Spatial preprocessing and statistical analysis were performed using SPM8 (Wellcome Department of Cognitive Neurology, Institute of Neurology, University College London, U.K.) and MATLAB version 2011b (MathWorks Inc., Natick, MA, USA). All FDG-PET images, both patient and control scans, were spatially normalized into the standardized stereotactic Montreal Neurological Institute space using our in-house FDG-PET template. This template was created following instructions introduced by Soma et al. [10]. A three-dimensional isotropic Gaussian kernel with 8 mm FWHM was used for smoothing all spatially normalized images. To remove the effect of global metabolism, we used global normalization with a proportional scaling method [11].

Table 1
Ratio of voxels in ROIs with statistically significant hypometabolism in the patient group relative to the control group, FDR adjusted p-value < 0.05.

ROI		ES		NES	
	ROI size	Significant		Significant	
	Voxels	Voxels	%	Voxels	%
Amygdala	192	28	14.58	0	0.00
Hippocampus	878	319	36.33	0	0.00
PHG	962	669	69.54	0	0.00
AHC	1578	744	47.15	0	0.00
TP	2563	1571	61.30	0	0.00
Insula	1134	632	55.73	54	4.76
OF	1175	861	73.28	90	7.66
GCA	795	35	4.40	113	14.21
GCM	1422	251	17.65	115	8.09
GCP	345	136	39.42	20	5.80
GCA + GCM	2296	300	13.07	248	10.80
Thalamus	972	307	31.58	114	11.73

ES – epileptogenic side, NES – nonepileptogenic side, PHG – parahippocampal gyrus, AHC – amygdalo-hippocampal complex, TP – temporal pole, OF – orbitofrontal cortex, GCA –anterior cingulate gyrus, GCM – middle cingulate gyrus, GCP – posterior cingulate gyrus.

2.8. Computing of statistic parametric maps

To lateralize the epileptogenic side (ES) to the left, we flipped 22 FDG-PET preprocessed images of right patients with MTLE (8 M, 14 F) in the direction of the x-axis.

For the group analysis, we used the Mann–Whitney *U* test and created parametric maps (PMs) using a voxelwise approach. We applied a false discovery rate (FDR) control for the results. In all analyses, FDR $q = 0.05$ was used as a level of statistical significance. These PMs were used in further analyses.

2.9. Comparison between different brain regions

To calculate the amount and the ratio of statistically significant voxels in different brain regions, an experienced neurologist selected 11 separate ROIs. These ROIs are presented in Table 1.

For each ROI for the ES and the nonepileptogenic side (NES), we created a mask using the WFU PickAtlas software toolbox (Functional MRI Laboratory, Wake Forest University School of Medicine, U.S.) [12] using the included automated anatomical labeling (AAL) atlas [13]. These masks were applied on the computed PMs of the whole brain to allow comparison between ROIs with different sizes. The ratio between the size of the ROI in voxels and the number of statistically significant voxels from the PMs matching this ROI was computed for all ROIs.

3. Results

3.1. SPM-PET analysis, comparison of patients with controls

By analyzing statistical parametric maps created using the Mann–Whitney *U* test, we found widespread statistically significant lower signal values (hypometabolism) in the patient group than in the control group, either on the ES or the NES. On the ES, the most pronounced hypometabolism was detected in the TP, parahippocampal gyrus, and amygdalo-hippocampal complex. Of the extratemporal sites on the ES, we observed the most pronounced hypometabolism in the orbitofrontal cortex and insula, followed by the thalamus and posterior cingulate gyrus. The most hypometabolism of the NES was observed in the thalamus and anterior cingulate gyrus and middle cingulate gyrus. All of our results are presented in Fig. 1; the ratios of significantly hypometabolic voxels on predefined ROIs on the ES and the NES are shown in Table 1. No significant differences between patients and controls were revealed in the TP, parahippocampal gyrus, or amygdalo-hippocampal complex on the NES (Fig. 1, Table 1).

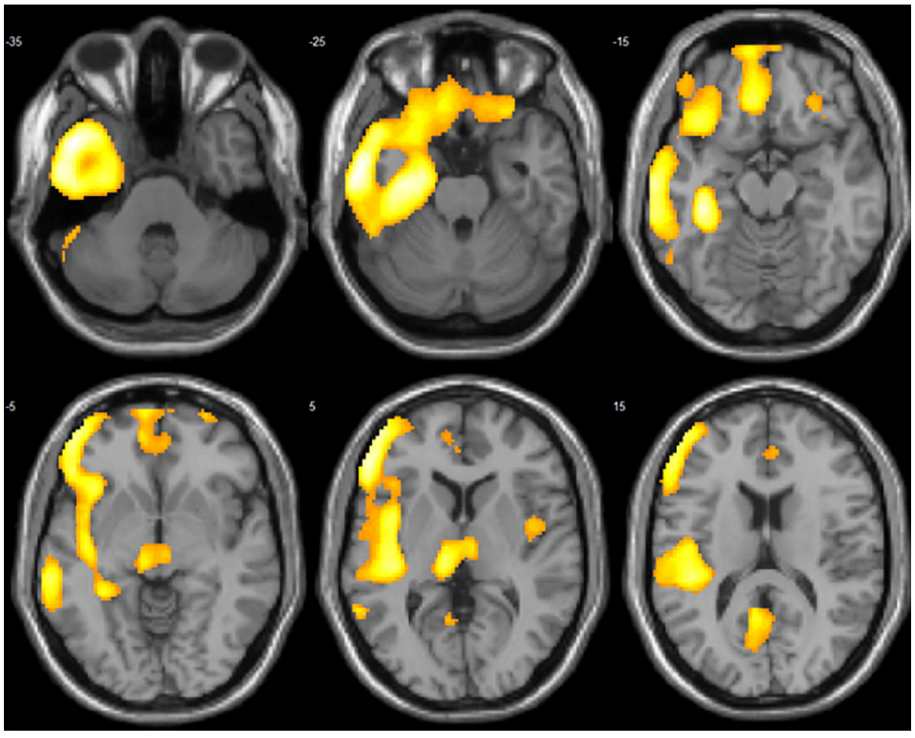

Fig. 1. Statistical parametric mapping of patients (N = 49) versus controls (N = 23) coregistered to T1 MRI. Epileptogenic side on the left showing large hypometabolism in the temoporal and extratemporal regions. False discovery rate adjusted p-value < 0.05.

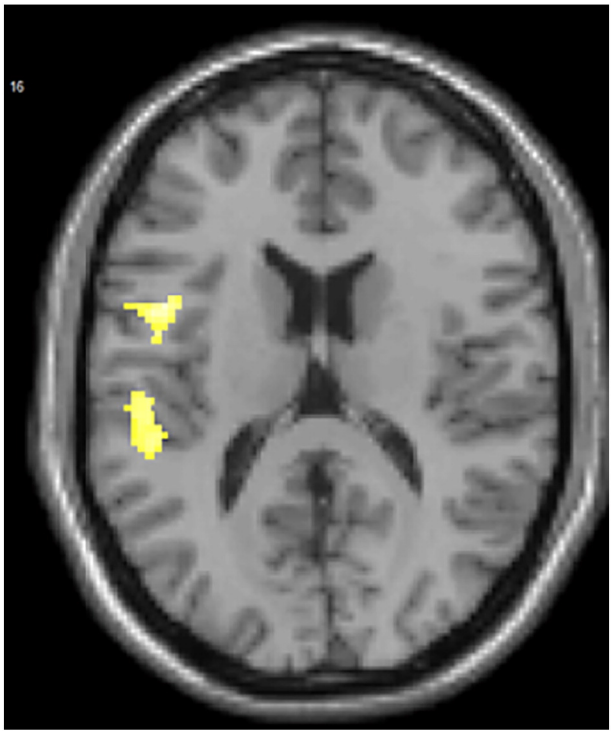

Fig. 2. Patients with severe hippocampal sclerosis Wyler grades 3 and 4 (N = 28) showing relative hypometabolism in the insula on the epileptogenic side as compared with the Wyler grades 1 and 2 group (N = 6). Coregistered to T1 MRI. False discovery rate adjusted p-value < 0.05.

3.2. SPM-PET analysis, comparison of patient groups

We did not find any significant differences between the right and left-sided patients with MTLE/HS after FDR correction.

We did not find any significant differences between patients with and without FCD in the TP, neither on the ES nor the NES. These groups differ in metabolism only in the posterior cingulate gyrus on the NES. In the group of patients with more severe HS (Wyler III/IV) (N = 28), we observed statistically significant hypometabolism in the insula on the ES in comparison with the patients classified as Wyler I/II (N = 6) (Fig. 2).

In patients with poor postoperative outcomes (ILAE III–V), we found statistically significant hypometabolism in the insula on the ES and on the NES in the TP and middle and posterior neocortex in comparison to the patients with better postoperative outcome (ILAE I/II) (Fig. 3).

The comparison of the patients with and without insult (encephalitis/meningoencephalitis and/or febrile seizures) in the history showed significant hypermetabolism in the TP either on the ES or the NES and in the middle temporal gyrus on the NES in patients with these insults in their history. The finding was more pronounced on the NES (Fig. 4).

Patients with longer epilepsy duration (>10 years) did not demonstrate any significant differences from patients with shorter duration (≤10 years).

4. Discussion

4.1. Comparison of patients with MTLE/HS to controls

Our study on patients with MTLE/HS clearly revealed very widespread hypometabolism of temporal regions (TP, parahippocampal gyrus, and amygdalo-hippocampal complex), extratemporal regions (orbitofrontal cortex, insula, posterior and anterior cingulate gyrus), and the thalamus. Glucose hypometabolism typically involved the temporal lobe ipsilateral to the HS, which is in agreement with previous studies using both visual and SPM analysis [14,15]. In the further text, we compare our results to results of another studies focusing on analysis of MTLE associated with HS proved by MRI or by histopathological finding. Some other studies have shown that hypometabolism often involves the extratemporal structures, mostly the ipsilateral frontal lobe and insula [16–18]. In addition to these finding, we observed hypometabolism on the side contralateral to HS in extratemporal regions, namely the anterior and middle cingulate gyrus. Another interesting finding in our study is the hypometabolism of subcortical areas. We did not observe any hypometabolism in the putamen, pallidum, or caudate nucleus, neither on the ES nor the NES. Nevertheless, we found the hypometabolism of the thalamus bilaterally to be more pronounced on the ES. Van Bogaert et al. [2] demonstrated hypometabolism in the ipsilateral and contralateral thalamus and

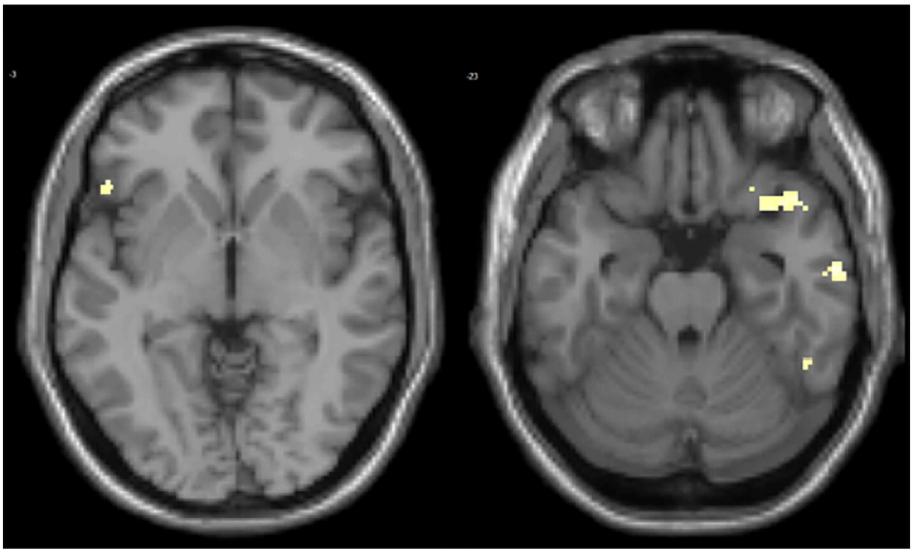

Fig. 3. ILAE classification 3 and 4 groups (N = 11) showing hypometabolism in the insula on the epileptogenic side and in the temporal lobe on the nonepileptogenic side relative to the ILAE 1 and 2 groups (N = 38) Coregistered to T1 MRI. False discovery rate adjusted p-value < 0.05.

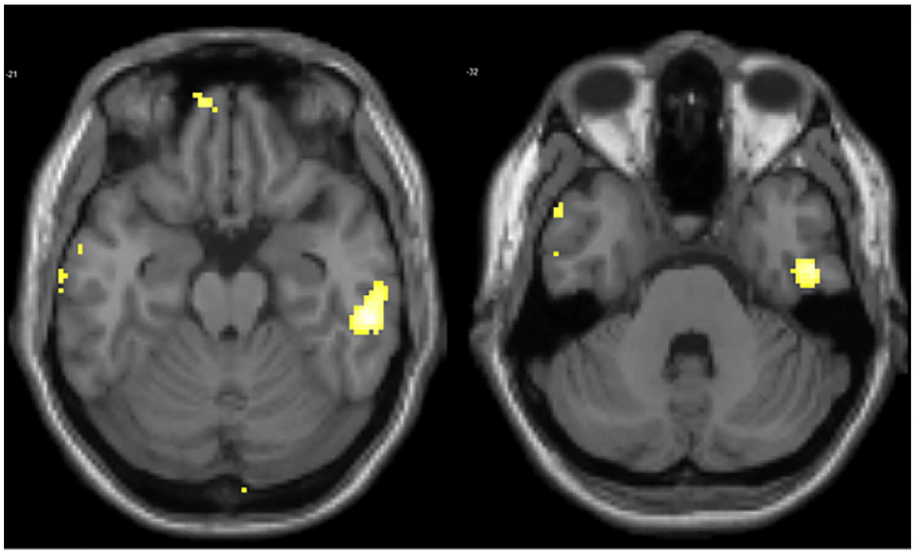

Fig. 4. Hypermetabolism on the nonepileptogenic side within the group of patients with encephalitis/meningoencephalitis and/or febrile seizures in the history (N = 21) compared with the group without any insult (N = 27). Corregistered to T1 MRI. False discovery rate adjusted p-value < 0.05.

caudate nucleus. Thalamic hypometabolism ipsilateral to the seizure side in patients with TLE was frequently reported in earlier studies using either visual or quantitative analysis [14,19,20]. Newberg et al., using SPM analysis, showed that hypometabolism, mostly of the contralateral thalamus, but also of the ipsilateral (to the epileptogenic side) thalamus, might be a predictor of poorer postoperative outcomes in patients with refractory TLE [21]. Thalamic hypometabolism probably correlates with the more widespread dysfunction of the temporal and extratemporal part of the limbic system that is observed in patients with refractory TLE. For future studies, it would be useful to determine which specific part of the thalamus shows the hypometabolism in these patients with TLE, i.e., for example in the anterior thalamic nuclei, which are part of the limbic system.

4.2. Comparison in relation to postoperative outcome

Our results clearly showed that patients with worse long-term postoperative outcomes had significant hypometabolism in the insula ipsilateral to the surgery and in the TP contralateral to the surgery, i.e., contralateral to HS. This finding might indicate a more pronounced bitemporal hypometabolism or a different pattern of hypometabolism outside the temporal lobe on the ES in comparison to patients with excellent postoperative outcome. We did not find statistically significant hypometabolism in the temporal lobe on the NES when comparing all patients and controls. Takahashi et al. [6] used a voxel-based comparison of FDG-PET to and controls and showed that significant hypometabolism in seizure-free patients preoperatively was restricted to the ipsilateral temporal tip and was not present in a postoperative nonseizure free group. Moreover, they showed that hypometabolism in the ipsilateral hippocampal, frontal, and thalamic areas were larger in the postoperative seizure-free group than in the nonseizure-free group. On the other hand, in the contralateral frontal and thalamic areas, the extents of hypometabolism were smaller in the seizure-free group than in the nonseizure-free group [6].

Studies focused on bilateral temporal hypometabolism showed relatively wide variability in terms of incidence, varying from 10 to 30% [22,23]. Previous studies using semiquantitative analysis showed that bilateral temporal hypometabolism is usually associated with bilateral temporal epilepsy, bilateral MRI findings, worse cognitive function, and bilateral independent seizure onset zones at the scalp EEG [22,24]. Another study revealed that bilateral temporal hypometabolism on FDG-PET in patients with MTLE is present in patients who had electrographic features, suggesting the early contralateral spread of ictal activity [17]. All of these variables might have a bad prognostic predictive value for seizure outcome in patients with TLE [23,25,26]. One recent study [27] showed that the duration from the last seizure could be an important factor that needs to be considered when analyzing the bitemporal involvement on interictal FDG-PET. Their multivariate analysis showed that bilateral temporal hypometabolism is significantly more often present when PET is performed within 2 days after the last seizure. Our study suggests that the finding of contralateral temporal hypometabolism on preoperative FDG-PET in a highly select group of patients with MTLE/HS is a negative prognostic factor for the postoperative outcome.

Concerning the finding of insular hypometabolism ipsilateral to the side of HS in patients with worse postoperative prognosis revealed by our study, we have to mention particularly the possible existence of "temporal-plus" (T+) epilepsies. This concept has been defined and analyzed in detail by some authors [28,29]. Temporal-plus epilepsies are very specific forms of seizures of multilobar origin which are characterized by the involvement of a complex epileptogenic network including the temporal lobe and the connected structures, mainly the orbitofrontal cortex, the insula, the frontal and parietal operculum, and the temporo-parieto-occipital junction. In general, patients with unifocal TLE are hardly distinguishable from the patients with T+ epilepsy on the basis of general clinical features or MRI data.

Furthermore, the presence of HS, which is known as one of the best prognostic factors for successful temporal lobe surgery [30,31], did not distinguish unifocal TLE from patients with T+ epilepsy. Only a minority of the patients in our series were investigated with invasive EEG, so we can only speculate that some of them might have T+ epilepsy, with the second focus in the insular cortex, which can very often be a part of the epileptogenic network in patients with MTLE/HS [28,29]. In conclusion, our results may indicate that hypometabolism in the insular cortex on preoperative FDG-PET using SPM analysis is a predictor of worse postoperative outcomes in patients with MTLE/HS and is an indication for invasive EEG in those patients.

4.3. Glucose metabolism in relation to histopathological findings

We demonstrated statistically significant hypometabolism in the insula on the ES in the group of patients with more severe HS (Wyler III/IV) in comparison with those with Wyler I/II classification. These groups did not differ in terms of postoperative outcome. This outcome

was even better in the group of patients with HS III/IV. Foldvary et al. [32] evaluated the neuronal density in mesiotemporal regions including the hippocampal subfield and correlated it with hypometabolism in the temporal lobe using a visual range scale. The neuronal density in CA1, CA4, subiculum, and dental granular cell layer did not correlate with the severity of the hypometabolism [32]. These data are supported by other studies evaluating the relationship between hippocampal cell density, hippocampal volume, and the degree of hypometabolism [33, 34]. On the other hand, Dlugos et al. [35] revealed that hilar cell densities correlated positively and significantly with hypometabolism in the bilateral thalamus, putamen, and globus pallidus, and in the ipsilateral caudate. Dentate granule cell densities correlated positively and significantly with hypometabolism in the bilateral thalamus and putamen. There was no significant correlation between cell densities and glucose metabolism in any cortical region, including the hippocampus [35]. Although these data are controversial, it might be postulated that hippocampal cell loss results in decreased efferent synaptic activity to the various cortical and subcortical regions resulting in subsequent hypometabolism.

We did not find significant differences between patients with or without FCD in the TP in any temporal lobe (both on the ES and the NES). These groups differ in metabolism only in the posterior cingulate gyrus on the NES. An isolated study analyzed this particular issue, demonstrating a different pattern of hypometabolism in patients with isolated HS and HS + FCD. The most prominent hypometabolism in HS patients was in the anterior and mesial parts of the temporal lobe; in patients with HS + FCD, it was in the lateral temporal lobe [36]. Out data are only marginally comparable to those data, because we used SPM analysis and the other study used an asymmetry index based on a comparison of the contralateral and ipsilateral side ROI counts, and because no patient in our series had FCD type II, whereas they were included in the other study.

4.4. Study limitations

While our method is based on statistical comparisons between groups, we have to rule out all outliers in the groups that may influence the results. Subjects with major brain malformations may not be correctly spatially normalized with the template image and the corresponding areas in analysis are not perfectly aligned, which may lead to incorrect results. In cases when a subject is missing a certain volume of brain tissue due to injury, disease, or surgery, the results of the analysis are focused in those missing volumes. Changes in metabolism in the remaining tissue thus cannot be revealed using this method. All subjects with such variance from the template image must be excluded from this type of analysis. Based on these criteria, two patients were removed from this study in order to not contaminate the findings.

We also suppose that this method could be beneficial in patient groups other than HS, i.e., in groups of nonlesional cases or of complicated cases with discordant presurgical data, but questions about the advantages of this method cannot be answered properly based on this study, because only patients with HS were included.

5. Conclusions

Our study shows that there are widespread significant changes in metabolism in patients with MTLE/HS in comparison to controls, either inside or outside the temporal lobe and mostly ipsilateral to the side of HS. These differences are most pronounced on the TP, the mesial part of the temporal lobe, and the orbitofrontal cortex ipsilateral to the side of HS. There are significant differences among these patients in terms of the postoperative outcome, degree of HS, and presence of insults in the patient history.

Acknowledgments

The authors would like to thank prof. Robert Kuba, who was the mentor of the first author until his premature death.

This research was carried out under the project CEITEC 2020 (LQ1601) with financial support from the Ministry of Education, Youth and Sports of the Czech Republic under the National Sustainability Programme II; by the project MEYS-NPS I-LO1413 and by the Ministry of Health, Czech Republic - conceptual development of research organization (MMCI, 00209805).

We thank Anne Johnson for grammatical assistance.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2017.11.014.

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Annex 9: Dolezalova I, Brazdil M, Chrastina J, Hemza J, Hermanova M, Janousova E, Pazourkova M, Kuba R. Differences between mesial and neocortical magnetic-resonance-imaging-negative temporal lobe epilepsy. Epilepsy & Behavior. 2016;62:21-26.

Epilepsy & Behavior 61 (2016) 21–26

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Differences between mesial and neocortical magnetic-resonance-imaging-negative temporal lobe epilepsy

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ARTICLE INFO

Article history:
Received 3 November 2015
Revised 8 April 2016
Accepted 11 April 2016
Available online 2 June 2016

Keywords:
MRI-negative temporal lobe epilepsy
Mesial MRI-negative TLE
Neocortical MRI-negative TLE
Clinical semiology
Invasive EEG
Semiinvasive EEG
Positron emission tomography

ABSTRACT

Objective: The aim of this study was to assess clinical and electrophysiological differences within a group of patients with magnetic-resonance-imaging-negative temporal lobe epilepsy (MRI-negative TLE) according to seizure onset zone (SOZ) localization in invasive EEG (IEEG).
Methods: According to SOZ localization in IEEG, 20 patients with MRI-negative TLE were divided into either having mesial SOZ–mesial MRI-negative TLE or neocortical SOZ–neocortical MRI-negative TLE. We evaluated for differences between these groups in demographic data, localization of interictal epileptiform discharges (IEDs), and the ictal onset pattern in semiinvasive EEG and in ictal semiology.
Results: Thirteen of the 20 patients (65%) had mesial MRI-negative TLE and 7 of the 20 patients (35%) had neocortical MRI-negative TLE. The differences between mesial MRI-negative TLE and neocortical MRI-negative TLE were identified in the distribution of IEDs and in the ictal onset pattern in semiinvasive EEG. The patients with neocortical MRI-negative TLE tended to have more IEDs localized outside the anterotemporal region ($p = 0.031$) and more seizures without clear lateralization of ictal activity ($p = 0.044$). No other differences regarding demographic data, seizure semiology, surgical outcome, or histopathological findings were found.
Conclusions: According to the localization of the SOZ, MRI-negative TLE had two subgroups: mesial MRI-negative TLE and neocortical MRI-negative TLE. The groups could be partially distinguished by an analysis of their noninvasive data (distribution of IEDs and lateralization of ictal activity). This differentiation might have an impact on the surgical approach.

1. Introduction

Patients with temporal lobe epilepsy (TLE) are the most common candidates for epilepsy surgery. There is a high probability that a patient with a lesional (MRI-positive) case will become seizure-free after surgery; the rates reach almost 80% in patients with hippocampal atrophy and concordant EEG findings [1]. In contrast, seizure-free rates are traditionally reported much lower in nonlesional or MRI-negative TLE. According to a meta-analysis, these rates may be 2.7 times lower than in lesional ones. For this reason, these patients are not considered to be good surgical candidates and are often excluded from surgical programs [2–7]. Studies focusing on MRI-negative TLE have been published in the past few years in which the surgical outcome seemed to be only slightly worse or even comparable to the lesional cases [8–15]. This is valid especially for patients with fluorodeoxyglucose positron emission tomography (FDG-PET) hypometabolism localized to one temporal lobe. In agreement with other noninvasive data, this subgroup is sometimes referred to as MRI-negative, PET-positive TLE [8–10,12–15].

The key point of surgery in MRI-negative TLE is to distinguish whether mesial or neocortical temporal lobe structures are primarily involved in seizure generation and, subsequently, to indicate the approach for appropriately tailored surgery. If this process is not performed correctly, the surgery does not result in seizure cessation and sometimes can even lead to serious memory decline, resulting in a patient with persistent seizures despite surgery and disabling memory problems [16]. The precise demarcation of cerebral tissue resection could be based on the findings of perioperative electrocorticography or chronic invasive EEG (IEEG), but the significance of perioperative electrocorticography remains controversial. There is still a very limited

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http://dx.doi.org/10.1016/j.yebeh.2016.04.027
1525-5050/

number of IEEG studies focusing on patients with MRI-negative TLE [14,15,17–20].

In this study, we divided patients with MRI-negative TLE according to the localization of their SOZ in IEEG into mesial MRI-negative TLE and neocortical MRI-negative TLE, and we tried to differentiate between these two types on the basis of their noninvasive data analysis.

2. Methods

2.1. Patient selection

This retrospective study included a total of 20 patients with MRI-negative TLE who underwent epilepsy surgery for refractory epilepsy at the Brno Epilepsy Center of Masaryk University Hospital between 2003 and 2013.

All patients underwent the IEEG procedure prior to surgery. Of the 20 patients, 18 (90%) were examined with chronically stereotactically implanted intracerebral electrodes. In one patient, we used a combination of stereotactically implanted intracerebral electrodes and subdural strip electrodes. In one other patient, the combination of one subdural strip and grid electrodes and intracerebral electrodes was used.

According to the localization of the SOZ in IEEG, patients were divided into mesial MRI-negative TLE (i.e., SOZ localized to the amygdala, hippocampus, and parahippocampal gyrus) or neocortical MRI-negative TLE. The study aimed to find differences between mesial and neocortical MRI-negative TLE based on the analysis of noninvasive data and semiinvasive EEG with the use of sphenoidal electrodes. The patients were compared on the following variables: demographic data, FDG-PET findings, interictal semiinvasive EEG, ictal semiinvasive EEG, and seizure semiology. Finally, patients with mesial MRI-negative TLE and patients with neocortical MRI-negative TLE were compared with regard to the results of surgical treatment and histopathological findings. The study was approved by the ethics committee of St. Anne's University Hospital.

2.2. Demographic data

Patient demographic data were obtained from patient charts. The following demographic data were analyzed: potential causes for the development of epilepsy, age at epilepsy onset, duration of epilepsy, frequency of complex partial seizures (CPSs) per month during the 6 months before surgery, and the presence/absence of a generalized tonic–clonic seizure (GTCS) in the 6 months before surgery.

2.3. FDG-PET scans

The FDG-PET images were acquired using a Siemens ECAT ACCEL PET scanner (three detection rings with lutetium-orthosilicate-type crystals and 16.2-cm axial FOV) (Erlangen, Germany) in 3-D mode using Brain protocol. The intrinsic spatial resolution of the scanner was 6.3 mm at full width at half maximum (FWHM) 1 cm from the center of the FOV and 6.7 mm at full width at half maximum 10 cm from the center of the FOV. The subjects fasted for 6 h before the scan and rested in a quiet, darkened room for 50–60 min after FDG administration. The dose of FDG administered was 200 MBq ± 15% per subject with no weight differentiation. The emission acquisition time in 3-D mode was 10 min. Forty-seven tomographic slices with a 3-mm slice thickness were reconstructed with a 128 × 128 iteration matrix with 6 iterations and 16 subsets and a 6-mm FWHM Gaussian filter applied.

The FDG-PET findings were analyzed visually by authors (I.D. and R.K.) experienced in reviewing FDG-PET scans of patients with epilepsy.

According to the localization of FDG-PET hypometabolism, patients were categorized to have the following:

1. hypometabolism on the operated side (Fig. 1);

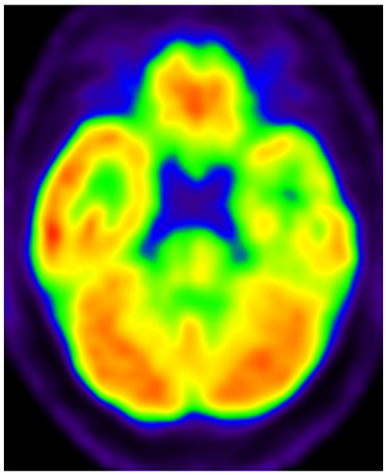

Fig. 1. FDG-PET with hypometabolism on operated side in patient with MRI-negative TLE.

2. hypometabolism on either side or hypometabolism contralateral to the operated side.

Patients with hypometabolism on the operated side were subdivided into having hypometabolism in the anterior and medial parts of the temporal lobe or in the lateral part of the temporal lobe.

2.4. Semiinvasive EEG

Semiinvasive EEGs were recorded based on the international 10–20 system with additional electrodes (anterotemporal T1, T2; sphenoidal Sp1, Sp2; and supraorbital SO1, SO2). The semiinvasive EEG was analyzed by two authors (I.D. and R.K.); discrepancies were resolved by consensus.

2.4.1. Semiinvasive EEG — interictal analysis

Five-minute samples from every hour of interictal EEG during the first 24 h were analyzed for the presence and distribution of IEDs.

According to IED distribution, patients were classified into the following:

1. unilateral IEDs (i.e., ≥90% of IEDs lateralized to the operated side) versus bilateral IEDs (i.e., <90% of IEDs lateralized to the operated side);
2. strictly anterotemporal IEDs versus also having extraanterotemporal IEDs on the operated side. Anterotemporal IEDs were described by phase reversal at Sp1/Sp2, T1/T2, or F7/F8.

2.4.2. Semiinvasive EEG — ictal analysis

According to the type of seizure onset pattern in semiinvasive EEG, the patients were classified as having all seizures correctly regionalized/lateralized over the operated temporal lobe versus having at least one seizure nonlateralized or falsely regionalized/lateralized. The definition of regionalized/lateralized seizure onset was published by Steinhoff et al. [21] and Risinger et al. [22].

2.5. Analysis of ictal semiology

The patient records were reviewed in order to analyze the type of aura. The following ictal signs were clinically evaluated during seizures: early oroalimentary automatisms (considered only if present within 20 s from the beginning of a seizure), early nonversive head turning, lateralized ictal immobility of the upper limb, ictal dystonia, rhythmic ictal nonclonic hand (RINCH) motions, periictal nose wiping, periictal face rubbing, periictal bed leaving, and periictal vegetative symptoms (retching with/without vomiting, coughing, urinary urge, water drinking; all were evaluated during the seizure and/or within 2 min after seizure

termination). Periictal nose wiping, periictal face rubbing, and periictal bed leaving were evaluated only in CPSs; other signs were evaluated in both CPSs and GTCSs. An ictal sign was counted as present in a patient if it was found in at least one of that patient's seizures.

2.6. Surgery and surgical outcome, neuropathological examination

The extent of the resection was based on the results of a presurgical evaluation. Surgical effectiveness was categorized at year 1 after surgery according to Engel classification as Engel I (no seizures, with or without nondisabling auras) or as Engel II–IV [23]. Focal cortical dysplasias (FCDs) were classified according to the classification system reported by Blümcke et al. [24].

2.7. Statistics

The differences in demographic data, patient characteristics, semiinvasive interictal/ictal EEG analysis, and clinical semiology between mesial MRI-negative TLE and neocortical MRI-negative TLE were calculated using the Mann–Whitney test or Fisher's exact test according to their condition of validity. For all tests, a p-value < 0.05 was considered statistically significant.

3. Results

3.1. The localization of the SOZ in IEEG

A total of 64 seizures were recorded by IEEG in 20 patients with MRI-negative TLE; the number of seizures per patient ranged from 1 to 5 (with an average of 3.3 ± 1.2). According to SOZ localization in IEEG, 13 of the 20 patients (65%) had mesial MRI-negative TLE, and 7 of the 20 patients (35%) had neocortical MRI-negative TLE. In patients with mesial MRI-negative TLE, 3 (15%) of the 13 showed alternating involvement of the temporal pole and mesial temporal lobe structures, with a majority of seizures originating in the mesial temporal lobe structures.

3.2. Demographic data

The age at epilepsy onset ranged from 0 to 36 years (with an average of 15.6 ± 9.7 years); the duration of epilepsy ranged from 3 to 41 years (with an average of 17.2 ± 11.1 years). The data concerning the main clinical features of the patients are summarized in Table 1. The SOZ was localized on the left side in 11 of the 20 patients (55%) and on the right side in 9 of the 20 (45%). No significant differences between mesial and neocortical MRI-negative TLE were found in age at epilepsy onset, duration of epilepsy, or side of the SOZ (Table 2).

Potential causes for the development of epilepsy were present in 9 of the 20 patients (45%). There were no statistically significant differences between patients with mesial and neocortical MRI-negative TLE in the absence/presence of potential causes for the development of epilepsy (Table 2).

The monthly CPS frequency during the 6 months before surgery ranged from 3 to 15 (with an average of 8.6 ± 3.7); GTCS during the 6 months preceding surgery were present in 13 of the 20 patients (65%). There were no statistically significant differences between mesial and neocortical MRI-negative TLE in the monthly CPS frequency or in the absence/presence of GTCS (Table 2).

3.3. FDG-PET scans

Of the 20 patients, 12 (60%) had FDG-PET hypometabolism on the operated side. The other 8 (40%) patients had no ipsilateral FDG-PET hypometabolism or contralateral hypometabolism. There were no statistically significant differences with respect to the localization of FDG-PET hypometabolism (hypometabolism on operated side vs. no hypometabolism or contralateral hypometabolism) between mesial and neocortical MRI-negative TLE ($p = 0.642$, Table 3). When analyzing the localization of hypometabolism on the operated side, the hypometabolism was present in the anterior and medial parts of the temporal lobe in 5 (39%) of the 13 patients with mesial MRI-negative TLE and in 3 (43%) of the 7 patients with neocortical MRI-negative TLE ($p = 1.000$).

Table 1
Main clinical features of 20 evaluated patients with MRI-negative TLE.

Patient no.	Localization of the SOZ (M/N)	Age at epilepsy onset (years)	Duration of epilepsy (years)	Frequency of CPSs per month	Occurrence of GTCS (+/−)	Potential cause	Side of operation (R/L)	Type of operation	Outcome (Engel I–IV)	Histopathological finding (FCD/MCD/negative)
1	Mes	16	11	3	−	ME	L	AMTR	I	Negative
2	Neo	11	14	10	+	Negative	R	Tailored cortectomy	I	Negative
3	Mes*	23	18	10	+	Negative	L	AMTR	II	FCD Ia
4	Mes	14	9	20	+	Negative	L	AMTR	IV	FCD Ib
5	Mes	36	11	8	+	Negative	L	AMTR	I	Negative
6	Mes	6	31	5	−	Negative	R	AMTR	III	Negative
7	Neo	11	14	15	−	Negative	L	Tailored cortectomy	IV	Negative
8	Mes	17	30	18	+	PT	R	AMTR	I	FCD Ia
9	Neo	17	10	12	−	ME	L	AMTR	I	FCD Ia
10	Mes*	1	40	5	−	ME	R	AMTR	IV	Negative
11	Mes	28	5	5	+	Trauma	R	AMTR	I	Negative
12	Neo	10	24	9	+	FS	R	AMTR	III	FCD Ia
13	Mes	0	41	3	+	Negative	L	AMTR	I	Negative
14	Neo	9	20	3	+	Negative	L	Tailored cortectomy	III	Negative
15	Mes*	3	23	10	+	Negative	L	AMTR	I	Negative
16	Neo	16	3	5	−	Negative	L	Resection of pole sparing hippocampus	IV	Negative
17	Mes	25	10	8	+	PT	R	AMTR	III	Negative
18	Neo	29	4	10	+	Trauma	R	AMTR + cortectomy	I	Negative
19	Mes	23	12	5	−	Negative	R	AMTR	III	Negative
20	Mes	17	14	8	+	PT	L	AMTR	I	Negative

AMTR — anteromesial temporal lobe resection, CPS — complex partial seizure, FCD — focal cortical dysplasia, FS — febrile seizure, GTCS — generalized tonic-clonic seizure, L — left, Mes — mesial, ME — meningitis/encephalitis, neo — neocortical, PT — perinatal trauma, R — right, SOZ — seizure onset zone.
* Seizure onset with alternating involvement of temporal pole and mesial temporal lobe structures.

Table 2
The differences in demographic data between mesial and neocortical MRI-negative TLE.

	Mesial (n = 13)	Neocortical (n = 7)	p-Value
Age at epilepsy onset (mean ± SD, min–max)	16.1 ± 11.1, 0–36	14.7 ± 7.0, 9–29	0.721
Duration of epilepsy (mean ± SD, min–max)	19.6 ± 12.2, 5–41	12.7 ± 7.8, 3–24	0.322
CPSs per month (mean ± SD, min–max)	8.3 ± 3–20	9.1 ± 3–15	0.423
Presence of GTCS, n (%)	9 (69)	4 (57)	0.651
Presence of potential insults, n (%)	6 (46)	3 (43)	1.000
– Encephalitis/meningitis, n (%)	2 (15)	1 (14)	
– Head injury, n (%)	1 (8)	1 (14)	
– Febrile seizures, n (%)	0 (0)	1 (14)	
– Perinatal trauma, n (%)	3 (23)	0 (0)	
Side of the SOZ — right, n (%)	6 (46)	3 (43)	1.000

CPS — complex partial seizure, GTCS — generalized tonic-clonic seizure, SOZ — seizure onset zone.

3.4. Semiinvasive EEG

3.4.1. Semiinvasive EEG — interictal analysis

When analyzing interictal semiinvasive EEG, 9 of the 20 patients (45%) exhibited predominantly unilateral IEDs; 11 of the 20 patients (55%) exhibited bilateral IEDs. There was no significant difference in IED distribution (unilateral vs. bilateral IEDs) between patients with mesial MRI-negative TLE and patients with neocortical MRI-negative TLE (Table 3).

The IEDs in an extraanterotemporal region were present in 5 of the 20 patients (25%): in 1 of the 13 patients (7.7%) with mesial MRI-negative TLE and in 4 of the 7 patients (57%) with neocortical MRI-negative TLE. This difference reached statistical significance (p = 0.031) (Table 3).

3.4.2. Semiinvasive EEG — ictal analysis

When analyzing semiinvasive ictal EEG, 7 of the 20 patients (35%) had all of their seizures correctly regionalized/lateralized; the other 13 of the 20 patients (65%) had at least one seizure either nonlateralized or falsely regionalized/lateralized. Seven of the 13 patients (54%) had all of their seizures correctly regionalized/lateralized in mesial MRI-negative TLE; this was true for none of the 7 patients (0%) with neocortical MRI-negative TLE. This difference was statistically significant (p = 0.044, Table 3).

3.5. Ictal semiology

Nineteen of the 20 patients (95%) exhibited an aura. Six (30%) had epigastric aura; another type of aura was present in the other 13 patients (65%) (Table 4). We did not find any significant differences between mesial MRI-negative TLE and neocortical MRI-negative TLE in the type of aura (epigastric vs. other).

A total number of 144 seizures (109 CPSs, 35 GTCSs; 80 seizures were recorded in semiinvasive EEG, the other 64 in IEEG) were available for clinical semiology evaluation; the number of evaluated seizures per patient ranged from 5 to 12 (with an average of 7.2 ± 1.8). The number of evaluated CPSs per patient ranged from 0 to 11 (with an average of 5.5 ± 2.3); the number of evaluated GTCSs per patient ranged from 0 to 5 (with an average of 1.85 ± 1.5).

We did not perform a statistical analysis of the semiology between patients with mesial MRI-negative TLE and patients with neocortical MRI-negative TLE because of the small number of patients, but it seemed that there were some signs more often associated with mesial seizure origin (early oroalimentary automatisms, early noninvasive head turning, RINCH) or lateral seizure origin (periictal face rubbing, Table 4).

Table 3
The differences in FDG-PET findings and semiinvasive EEG between mesial and neocortical MRI-negative TLE.

	Mesial (n = 13)	Neocortical (n = 7)	p-Value
FDG-PET findings			
Clearcut hypometabolism, n (%)	7 (54)	5 (71)	0.642
Interictal analysis			
Unilateral IEDs, n (%)	5 (38)	4 (57)	0.642
Bilateral IEDs, n (%)	8 (62)	3 (43)	
Extraanterotemporal IEDs, n (%)	1 (8)	4 (57)	0.031
Ictal analysis			
All seizures correctly regionalized/lateralized, n (%)	7 (54)	0 (0)	0.044
At least 1 seizure nonlateralized or falsely regionalized/lateralized, n (%)	6 (46)	7 (100)	

IEDs — interictal epileptiform discharges.

Table 4
The differences in clinical semiology between mesial and neocortical MRI-negative TLE.

	Mesial (n = 13)	Neocortical (n = 7)	p-Value
Type of aura			
Epigastric aura, n (%)	4 (31)	2 (29)	1.000
Other type, n (%)	9 (69)	5 (71)	
Clinical semiology			
Early oroalimentary automatisms, n (%)	7 (54)	2 (29)	
Early nonversive head turning, n (%)	10 (77)	3 (43)	
Immobility of the upper limb, n (%)	6 (46)	2 (28)	
Ictal dystonia, n (%)	3 (23)	2 (29)	
RINCH, n (%)	4 (31)	0 (0)	
Periictal nose wiping, n (%)	9 (69)	5 (71)	
Periictal face rubbing, n (%)	6 (46)	6 (86)	
Periictal bed leaving, n (%)	3 (23)	2 (29)	
Retching, n (%)	2 (15)	0 (0)	
Coughing, n (%)	6 (46)	2 (29)	
Urinary urge, n (%)	2 (15)	1 (14)	
Water drinking, n (%)	2 (15)	0 (0)	

RINCH — rhythmic ictal nonclonic hand motions.

3.6. Surgery and surgical outcome

Standard anteromesial temporal lobe resection (AMTR) was performed in 14 patients (70%), tailored cortectomy of the lateral temporal cortex in 3 (15%), AMTR plus tailored cortectomy of the lateral temporal cortex in 2 patients (10%), and resection of the temporal pole sparing the hippocampus in 1 patient (5%).

When analyzing surgical outcome at year 1 after surgery, 12 of the 20 patients (60%) were characterized as Engel I and the other 8 (40%) as Engel II–IV (1 patient Engel II, 4 patients Engel III, 3 patients Engel IV). There were no significant differences in surgical outcome at year 1 after surgery between mesial MRI-negative TLE and neocortical MRI-negative TLE, but the tendency of mesial MRI-negative TLE to result in better surgical outcome was present (Table 5).

Table 5
The differences in histopathological findings and in surgical outcome at year 1 after surgery defined on the basis of Engel classification between mesial and neocortical MRI-negative TLE.

	Mesial (n = 13)	Neocortical (n = 7)	p-Value
Outcome			
Engel I, n (%)	9 (69)	3 (42)	0.356
Engel II–IV, n (%)	4 (31)	4 (57)	
Histopathological findings			
Negative, n (%)	10 (77)	5 (71)	1.000
FCD, n (%)	3 (23)	2 (29)	

FCD — focal cortical dysplasia.

3.7. Histopathological findings

The histopathological findings were negative in 15 of the 20 patients (75%); FCD was present in 5 patients (25%) (FCD Ia was present in 4 of the 5 patients (80%) with FCD; FCD Ib was present in 1 of the 5 patients (20%) with FCD). There were no statistically significant differences in histopathological findings between mesial MRI-negative TLE and neocortical MRI-negative TLE (Table 5).

4. Discussion

Patients with MRI-negative TLE represent a distinct subgroup of the patients with nonlesional epilepsy — they differ from the others because of a relatively good surgical outcome, and therefore, they come to the forefront of many centers for epilepsy surgery [8,12–14,25,26]. On the basis of MRI and FDG-PET, Carne et al. described a group of patients with MRI-negative, PET-positive TLE. This patient type was subsequently characterized in detail by other authors [8–10,12,13]. For patients with MRI-negative, PET-positive TLE, FDG-PET hypometabolism is typical, which correlates with interictal and ictal electrophysiological findings, and these patients had excellent surgical outcomes. In our study of MRI-negative TLE, 60% of the patients had characteristic FDG-PET hypometabolism that corresponded to the side of operation; the remaining 40% of the patients had either no findings on FDG-PET or the hypometabolism was lateralized to the nonoperated side. This is in agreement with the study by Lee et al. in which a correlation of hypometabolism on PET and side of resection was described in 59% of patients [14].

Patients with MRI-negative TLE can be classified according to the localization of their SOZ as mesial MRI-negative TLE or neocortical MRI-negative TLE. In our study, 65% of the patients were classified as having mesial MRI-negative TLE, and 35% of the patients were classified as having neocortical MRI-negative TLE. Luther et al. stated that 25% of patients have neocortical MRI-negative TLE [17]. In a study by Lee et al., a group of 32 patients with MRI-negative TLE was analyzed, with 25% of the patients having “pure” neocortical seizure onset, 38% of the patients having “pure” mesial seizure onset, and the rest of the patients with independent or simultaneous mesial and neocortical seizure onset [14].

In our analysis, we tried to find differences between mesial and neocortical MRI-negative TLE based on noninvasive and semiinvasive data analysis. These differences might be helpful in surgery planning, as they could distinguish between patients who could proceed directly to surgery and patients in whom IEEG or perioperative electrocorticography is necessary. In our study, we found differences based on semiinvasive EEG analysis, namely different distribution of IEDs and different ictal onset pattern. In the literature, there are also references about different ictal semiology between patients with mesial MRI-negative TLE and patients with neocortical MRI-negative TLE [14].

In our study, extraanterotemporal IEDs were found in approximately 25% of the patients. We found a statistically significantly higher incidence of extraanterotemporal IEDs in patients with neocortical MRI-negative TLE than in patients with mesial MRI-negative TLE (57% vs. 8%). In the past, the predominance of lateral neocortical IEDs was reported to be associated with lesional neocortical TLE [27].

When analyzing ictal onset patterns in semiinvasive EEG, we found that only 35% of the patients had all of their seizures correctly lateralized; the remaining 65% of the patients had at least one seizure nonlateralized or falsely regionalized/lateralized. We found that patients with mesial MRI-negative TLE had all of their seizures correctly lateralized more often than patients with neocortical MRI-negative TLE (54% vs. 0%). This difference is also supported by literature focusing on lesional TLE. In a study by O'Brien et al., almost 80% of patients with neocortical TLE had bilateral ictal activity at onsets, compared to almost 50% of patients with mesial TLE [28]. According to the results, we believe that the lateralization of ictal activity at the beginning of seizures and the distribution of IEDs could be an indicator of SOZ localization and a red flag for surgery, but the possibility of unequivocal localization (mesial vs. neocortical) seems to be limited.

We did not find any significant differences in demographic data (age at epilepsy onset, duration of epilepsy, frequency of CPSs, the presence/absence of GTCS, the presence of potential insults for the development of epilepsy, or side of the SOZ) between patients with mesial MRI-negative TLE and patients with neocortical MRI-negative TLE. No differences in a group of patients with lesional TLE between mesial and neocortical TLE were reported with respect to seizure frequency, proportion with GTCS, or epilepsy history [27,28]. The only characteristic of lesional mesial TLE is the occurrence of febrile seizures by medical history, which is conditioned by the fact that the febrile seizure is a known risk factor for hippocampal sclerosis development [29,30]. Similarly to other authors, we found only a very low number of patients with FS (approximately 5% of patients exhibited FS in both studies) [8].

We did not prove any significant differences in the representation of bilateral IEDs between mesial and neocortical MRI-negative TLE. The same results were reported by other authors analyzing interictal EEG differences between mesial and neocortical MRI-negative and lesional TLE [14,28,31].

In the literature, some ictal semiology features are associated with mesial seizure onset (i.e., epigastric aura, ipsilateral limb automatism, contralateral dystonic posturing, and oroalimentary automatisms) and others with neocortical seizure onset (i.e., psychic, auditory, and visual aura and early aphasia) [29,32–36]. A study by Lee et al. focusing on differences between mesial and neocortical MRI-negative TLE reported a difference in clinical semiology that reached statistical significance [14]. All of the patients with exclusively neocortical temporal seizure onset had typical neocortical temporal semiology in comparison to patients with mesial and independent or simultaneous mesial and neocortical seizure onset. We observed similar tendencies in our study. On the other hand, there are also studies which did not find any statistically significant difference in semiology between mesial and neocortical TLE [28].

As mentioned at the beginning of this section, MRI-negative TLE is characterized by a better surgical outcome than other nonlesional types of epilepsy, especially in cases of MRI-negative, PET-positive TLE. LoPinto-Khoury et al. reported that 76% of patients with MRI-negative, PET-positive TLE are classified as Engel I in year 2 and 75% in year 5 after surgery [12]. In a study by Carne et al., the surgical outcome in patients with MRI-negative, PET-positive TLE was even slightly better than in patients with hippocampal sclerosis [8]. In a study published by Kuba et al. analyzing patients with MRI-negative, PET-positive TLE who had surgery in our department, 71% of the patients were classified as Engel I at the final follow-up [13]. In our present study, 60% of patients were postoperatively classified as Engel I in year 1 after surgery. Our results are in agreement with two studies focusing on MRI-negative TLE: Lee et al. (who reported Engel class I in 65% of patients) and Burkholder et al. (who reported Engel class I in 55% of patients) [14,15].

When looking at differences in surgical outcome between mesial and neocortical MRI-negative TLE, we found that patients with mesial MRI-negative TLE tended to have better surgical prognosis than patients with neocortical MRI-negative TLE (69% seizure-free vs. 42%), but these results did not reach statistical significance. Similar results were published by Lee et al.: seizure freedom was attained in 70% of patients with mesial temporal onset and in 33% of patients with neocortical seizure onset [14].

In our study, 75% of the patients had negative histopathological findings, and the remaining 25% of the patients exhibited signs of FCD. The Negative histopathology seems to be common in MRI-negative TLE [8,11]. Carne et al. found FCD in 10% of the patients and HS in 10% of the patients [8]. Similar results were published by Immonem et al., who found negative histopathological findings in 68% of patients with nonlesional TLE; there were HS, signs of gliosis in the hippocampus/amygdala, oligodendroglioma, and dysembryoplastic neuroepithelial tumor (DNET) in the remaining 32% of the patients in

their study [11]. We did not prove any statistically significant differences in pathology between patients with mesial and neocortical MRI-negative TLE.

The biggest limitation of our study is the small sample size of 20 patients with MRI-negative TLE. In such a small group, it is probable that we missed some of the differences. We believe that there are distinctions between mesial MRI-negative TLE and neocortical MRI-negative TLE with respect to seizure semiology and to surgical outcome, but we were not able to prove them statistically. The other problems of our study are its retrospective design and the "purity" of the group with mesial MRI-negative TLE, in which 15% of the patients had seizure onset alternating between the area of the temporal pole and mesial temporal lobe structures.

5. Conclusions

In conclusion, approximately two-thirds of patients with MRI-negative TLE have the seizure onset localized to the mesial temporal lobe structures, and one-third have the seizure onset localized to the neocortical areas. Noninvasive data, specifically the distribution of IEDs and the lateralization of ictal activity, contain some features which help distinguish between mesial and neocortical MRI-negative TLE. Patients with mesial MRI-negative TLE tend to have IEDs more restricted to the anterotemporal area and to have all of their seizures clearly lateralized into one temporal lobe. Despite these findings, it seems that only IEEG is able to provide adequate information about precise SOZ localization, which is essential for surgery. Only a correctly tailored resection can result in seizure freedom in a given patient with a minimal risk of a cognitive decline [14]. If we manage to localize the SOZ correctly in patients with MRI-negative TLE, almost 60% of patients can become seizure-free after the surgery, which is higher than in other types of nonlesional epilepsies and almost comparable to lesional ones.

Acknowledgments

We would like to thank Anne Johnson for grammatical assistance.

This work was supported by the project "CEITEC — Central European Institute of Technology" (CZ.1.05/1.1.00/02.0068) from the European Regional Development Fund.

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Annex 10: Rehulka P, **Dolezalova I**, Janousova E, Tomasek M, Marusic P, Brazdil M, Kuba R. Ictal and postictal semiology in patients with bilateral temporal lobe epilepsy. Epilepsy & Behavior. 2014;41:40-46.

Epilepsy & Behavior 41 (2014) 40–46

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Ictal and postictal semiology in patients with bilateral temporal lobe epilepsy

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ARTICLE INFO

Article history:
Received 11 July 2014
Revised 7 September 2014
Accepted 10 September 2014
Available online 1 October 2014

Keywords:
Epilepsy
Bitemporal
Bilateral temporal lobe epilepsy
Invasive EEG
Semiology
Postictal unresponsiveness

ABSTRACT

Bilateral temporal lobe epilepsy is characterized by evidence of seizure onset independently in both temporal lobes. The main aim of the present study was to determine whether patients with evidence of independent bilateral temporal lobe epilepsy (biTLE) can be identified noninvasively on the basis of seizure semiology analysis. Thirteen patients with biTLE, as defined by invasive EEG, were matched with 13 patients with unilateral temporal lobe epilepsy (uniTLE). In all 26 patients, the frequency of predefined clusters of ictal and periictal signs were evaluated: ictal motor signs (IMSs), periictal motor signs (PIMSs), periictal vegetative signs (PIVSs), the frequency of early oroalimentary automatisms (EOAs), and the duration of postictal unresponsiveness (PU). Some other noninvasive and clinical data were also evaluated. A lower frequency of IMSs was noted in the group with biTLE (patients = 46.2%, seizures = 20.7%) than in the group with uniTLE (patients = 92.3%, seizures = 61.0%) ($p = 0.030$; $p < 0.001$, respectively). The individual IMS average per seizure was significantly lower in the group with biTLE (0.14; range = 0–1.0) than in the group with uniTLE (0.80; range = 0–2.6) ($p = 0.003$). Postictal unresponsiveness was longer than 5 min in more patients (75.0%) and seizures (42.9%) in the group with biTLE than in the group with uniTLE (patients = 30.8%, seizures = 18.6%) ($p = 0.047$; $p = 0.002$). The frequency of EOAs, PIMSs, PIVSs, and other clinical data did not differ significantly. There is a lower frequency of ictal motor signs and longer duration of postictal unresponsiveness in patients with biTLE.

1. Introduction

Bilateral temporal lobe epilepsy or also known as bitemporal epilepsy is often vaguely characterized by the existence of independent seizure-onset zones in both temporal lobes. Bitemporal epilepsy is not clearly defined and is usually suspected when independent bilateral temporal seizures are recorded in scalp EEG. Bitemporal epilepsy has been defined by depth electrodes, as clear clinical and scalp EEG differences that could noninvasively distinguish bitemporal epilepsy from unilateral temporal lobe epilepsy have not been established [1]. Patients with bitemporal epilepsy are generally considered to be poorer surgery candidates than patients with unilateral temporal lobe epilepsy [2–5]. Seizure semiology is an important part of the presurgical assessment of epilepsy surgery candidates. To the best of our knowledge, the seizure semiology in bitemporal epilepsy and that in unilateral temporal lobe epilepsy have not been compared in detail. The main goal of this study was to reveal potential differences between the patients with bitemporal epilepsy and those with unilateral temporal lobe epilepsy in terms of history data, semi-invasive EEG findings, and seizure semiology.

2. Methods

2.1. Group definition

We reviewed all of the patients with temporal lobe epilepsy (TLE) who underwent invasive video-EEG at one of two epilepsy centers in Czech Republic: the Brno Epilepsy Center at St. Anne's University Hospital between 1999 and 2012 and the Epilepsy Center Motol at the University Hospital Motol in Prague between 2006 and 2012. We defined the following criteria for identifying the patients in the group with bitemporal epilepsy (biTLE): independent bitemporal seizure origin, defined on the basis of invasive EEG as (1) spontaneous clinical seizures arising independently from both temporal lobes (electrographic

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http://dx.doi.org/10.1016/j.yebeh.2014.09.033
1525-5050/

seizures were not included in this analysis because their clinical significance is not yet clearly determined [6]) and/or (2) habitual complex partial seizures (CPSs) elicited by the electrical stimulation of the temporal lobe contralateral to the spontaneous seizures. For comparison purposes, we formed a control group of patients with unilateral temporal lobe epilepsy (the group with uniTLE). The subjects in this group were patients with uniTLE who were completely seizure-free for at least two years after epilepsy surgery. Patients from the group with uniTLE were matched with patients from the group with biTLE in terms of age at the onset of epilepsy, age at evaluation, duration of epilepsy, and gender. We selected a group of 26 patients who fulfilled these matching criteria (13 in the group with biTLE and 13 in the group with uniTLE). The study was approved by the Ethics Committee of St. Anne's University Hospital.

2.2. Presurgical evaluation

All 26 patients underwent a comprehensive presurgical evaluation, including detailed history and neurological examination, neuropsychological testing, magnetic resonance imaging (MRI), and scalp video-EEG monitoring. Bilateral carotid sodium amobarbital/methohexital testing was performed in 11 patients of the group with biTLE and 12 patients of the group with uniTLE; unilateral testing was available in one patient of the group with biTLE. Interictal and/or ictal single-photon emission computed tomography (SPECT) was performed in 10 patients of the group with biTLE and in seven patients in the group with uniTLE. Fluorodeoxyglucose positron emission tomography (FDG-PET) was performed in 12 patients from the group with biTLE and in seven patients from the group with uniTLE.

2.3. Scalp EEG, semi-invasive EEG, and invasive EEG procedures

In all 13 patients in the group with biTLE, invasive video-EEG monitoring was a part of the presurgical evaluation. In the patients from the group with uniTLE, depth EEG was performed in four patients because their noninvasive data were insufficient to proceed directly to surgery. Evidence indicates that all 26 patients had mesial temporal lobe epilepsy: in all of the patients in the group with biTLE and in four of the patients from the group with uniTLE who underwent invasive EEG (patients 14, 15, 18, and 23), the seizure-onset zone (SOZ) was found within the hippocampus, amygdala, or temporal pole (i.e., anteromesio-temporal onset) (see Table 1); in the remaining nine patients from the group with uniTLE (patients 16, 17, 19, 20, 21, 22, 24, 25, and 26) the lesion localization, long-term video-EEG monitoring with scalp/sphenoidal electrodes, and FDG-PET findings led us to consider them to be patients with mesial temporal lobe epilepsy.

Scalp/sphenoidal EEG was performed using the international 10–20 electrode placement system. Multicontact depth electrodes inserted orthogonally or diagonally into both amygdalohippocampal complexes were used in all patients of the group with biTLE. A combination of two stereotactically implanted depth electrodes and subdural strip electrodes was used in two patients (patients 12 and 13).

Only preoperative EEG data were used for further analysis in all of the patients.

2.4. Surgery and outcome measure

Eight patients from the group with biTLE and all of the patients from the group with uniTLE underwent resective surgery. We recorded the

Table 1
Demographic and clinical characteristics, histopathology, and outcome in the group with biTLE (patients: 1–13) and in the group with uniTLE (patients: 14–26). M — male; F — female; TBI — traumatic brain injury; PI — perinatal insult; FSs — febrile seizures; M/E — meningitis/encephalitis; LD — language dominance according to the Wada test; L — left; R — right; * — only unilateral testing performed; SOZ — localization of seizure-onset zone proven by invasive EEG (if performed); AHC — amygdalohippocampal complex; Tpol — temporal pole; HS — hippocampal sclerosis; DNET — dysembryoplastic neuroepithelial tumor; TL — temporal lobe; MCD — malformation of cortical development; HA — hippocampal atrophy; MAng — meningioangiomatosis; HIMAL — hippocampal malrotation; FCD — focal cortical dysplasia; VNS — vagus nerve stimulation; AMTR — anteromedial temporal lobe resection; LE — lesionectomy.

Patient	Sex/age at evaluation (years)	Insult	LD	Side-SOZ identified by invasive EEG	MRI finding	Side/surgery	Histopathology	Follow-up surgery (years)	Follow-up VNS (years)	Outcome (Engel)	Outcome (Mc Hugh)
Bitemporal group											
1	M/33	TBI	L	L-AHC; R-AHC	Normal	–	–	–	14	–	I
2	M/41	PI, FSs	L	L-AHC; R-AHC	HS	L/AMTR	HS grade IV	3	2	III A	V
3	F/29	–	L	R-AHC; L-AHC	Tumor	R/AMTR	DNET	3	–	I B	–
4	F/25	–	L	R-AHC; L-AHC	AHC hyperintensity	R/AMTR	Gliosis	10	–	I A	–
5	M/23	–	L	L-Tpol, AHC; R- AHC	TL hypotrophy	L/AMTR	FCD IA	2	1	IV	V
6	F/19	–	L	L-Tpol, AHC; R- AHC	Normal	L/temporal pole resection	Normal	2	1	IV	III
7	F/41	M/E	L	R-AHC; L-AHC	HS	R/AMTR	HS grade III	2	–	II A	–
8	F/33	–	L*	R-AHC; L-AHC	MCD	–	–	–	2	–	V
9	M/47	PI	–	L-AHC; R-AHC	HA	–	–	–	2	–	II
10	F/51	–	L	R-AHC; L-AHC	TL lesion	R/AMTR	MAng	1	–	III A	–
11	F/29	PI	L	R-AHC; L-AHC	HIMAL	–	–	–	4	–	V
12	M/41	–	L	L-Tpol, AHC; R-AHC	Suspected FCD	L/AMTR	FCD IA	5	–	IV	–
13	M/43	PI, M/E	L	L-Tpol, AHC; R-AHC	HS	–	–	–	–	–	–
Unitemporal group											
14	M/33	–	L	R-AHC	HA	R/AMTR	Normal	9	–	I A	–
15	M/29	PI, FSs	–	–	HS	R/AMTR	HS grade uncertain	10	–	I A	–
16	M/41	M/E, FSs	L	L-AHC	HS	L/AMTR	HS grade uncertain	9	–	I A	–
17	M/21	PI	L	–	HA	L/AMTR	Normal	3	–	I A	–
18	F/41	–	L	L-AHC	Normal	L/AMTR	FCD IA	3	–	I A	–
19	M/40	–	L	–	Cavernoma	R/extended LE	Cavernoma	9	–	I A	–
20	F/36	PI, FSs	L	–	HS	R/AMTR	HS grade uncertain	8	–	I A	–
21	M/31	–	L	–	HS	L/AMTR	HS grade III	7	–	I A	–
22	F/24	–	L	–	Tumor	R/extended LE	DNET	9	–	I A	–
23	F/47	–	L	L-AHC	Normal	L/AMTR	Normal	2	–	I A	–
24	M/33	–	L	–	Normal	R/AMTR	Normal	5	–	I A	–
25	M/43	–	L	–	Normal	R/AMTR	FCD IA	3	–	I A	–
26	M/36	M/E	L	–	HA	L/AMTR	Normal	4	–	I A	–

seizure outcome at the last follow-up visit for all of the patients and classified them based on Engel's classification [7]. Individual features, including side of surgery, follow-up duration, and outcome at the most recent follow-up visit, are presented in Table 1.

2.5. VNS procedure and outcome measure

Five patients from the group with biTLE received vagus nerve stimulation (VNS). The implantation procedure was performed in a standardized manner and under general anesthesia. We recorded the seizure reduction at the most recent follow-up visit for all of the patients and classified them based on the McHugh classification for measuring the efficacy of VNS [8]. Individual follow-up duration and outcome at the most recent follow-up visit are mentioned in Table 1.

2.6. Histopathological examination

A histopathological examination was performed on patients who underwent resective surgery. If focal cortical dysplasia was present in the temporopolar region, the recent ILAE classification system [9] was used; proven cases of hippocampal sclerosis were classified according to the classification of Wyler [10].

2.7. Clinical variables

Anamnestic data were collected using a retrospective review of the medical records, including the presence or absence of insults prior to the development of the epilepsy such as traumatic brain injury, history of perinatal insult, history of febrile seizures, history of central nervous system infection (i.e., meningitis or encephalitis), anamnestic experience of aura, the presence of <1 or ≥ 1 secondarily generalized tonic–clonic seizure(s) (GTCS(s)) per year (at time of study), and total seizure frequency per month (TSF) calculated as the mean frequency during the six months prior to the preoperative evaluation.

2.8. Semi-invasive ictal EEG parameters

Ictal EEGs were analyzed independently by two authors of this study (PR and ID); disagreements, if present, were resolved by consensus. The following ictal parameters were evaluated:

- Seizure onset (SO) — defined as the time when the first unequivocal change in patient behavior or in EEG appeared, depending on whether EEG or behavioral change developed first;
- Presence of early rhythmic theta/alpha activity (ERTA) — considered as a rhythmic 4- to 8-Hz activity present in scalp/sphenoidal electrodes Sp1, Sp2, T1, and T2 within 20 s from the SO;
- Time to the development of rhythmic theta/alpha activity (TRTA) — defined as the time from the SO to the development of rhythmic 4- to 8-Hz activity in scalp/sphenoidal electrodes Sp1, Sp2, T1, and T2;
- Bitemporal propagation time (BPT) — defined as the time from the SO to the propagation of rhythmic ictal activity to at least one of the contralateral electrodes Sp1, T1, T3 or Sp2, T2, T4;
- Ictal activity duration (IAD) — defined as the time from the SO to the end of the ictal activity (EIA), i.e., to the replacement of rhythmic ictal activity with irregular slowing or diffuse attenuation without any rhythmic ictal activity within all scalp/sphenoidal electrodes.

2.9. Seizure semiology

Scalp, semi-invasive, and invasive ictal video-EEG recordings were assessed, and the following ictal and periictal signs were evaluated:

- Early oroalimentary automatisms (EOAs) — defined as repetitive movements of the mouth, such as mastication, swallowing, lip smacking, or blowing, considered only if present within 20 s from the SO
- Ictal motor signs (IMSs) occurring during the ictal period of CPSs, which included the following:
  - Early nonversive head turning — defined as a natural and unforced lateral movement of the head within first 30 s after the SO [11]
  - Lateralized ictal immobility of the upper limb — defined as a condition lasting more than 10 s in which one of the upper extremities performs no movement and rests in a natural position next to the body without visually detected dystonic or tonic posturing, while the second upper limb demonstrates movement [12]
  - Ictal dystonia — defined as an unnatural posture of one upper extremity associated with the rotatory component [13]
  - Rhythmic ictal nonclonic hand (RINCH) motions — defined as unilateral, rhythmic, nonclonic, nontremor motions of an upper extremity or opening–closing motions of the hand lasting more than 5 s [14]
- Periictal vegetative symptoms (PIVSs), which included retching with/without vomiting, cough, urinary urge, and water drinking; all during a seizure and/or within 2 min after seizure termination, as defined by EIA [15]
- Periictal motor signs (PIMSs), which included the following:
  - Periictal nose wiping or face rubbing — defined as the movement of one upper extremity directed to the face, rubbing of the nose during the seizure or within 2 min after seizure termination, as defined by EIA [16]
  - Periictal bed leaving — defined as lateralized leaving from bed during seizures or within 3 min after seizure termination, as defined by EIA [17]

  EOAs, IMSs, and PIVSs were analyzed both in CPSs and GTCSs; PIMSs only in CPSs
- Postictal unresponsiveness (PU), which was analyzed only in CPSs and defined as the time from the end of EEG ictal activity to the recovery of normal contact, i.e., contact without impaired speech and without confusion. We used this definition because, usually, it is not possible to distinguish unequivocally between postictal dysphasia and postictal confusion in all seizures. The duration of PU was categorized according to its duration as short ($\leq$3 min), medium (3–5 min), and long ($>$ 5 min).

2.10. Statistical analysis

The distribution of clinical variables was compared between the group with biTLE and that with uniTLE using the nonparametric Mann–Whitney test or Fisher's exact test according to their condition of validity. For all tests, p value < 0.05 was considered statistically significant. For TRTA, BPT, IAD, and IMSs, we calculated the individual average for each patient, and then we calculated the median of individual values for the group with biTLE and that with uniTLE because the individual values in both groups did not have a normal distribution.

Table 2
Clinical characteristics of the group with biTLE and that with uniTLE; GTCSs — generalized tonic–clonic seizures; TSF — total seizure frequency per month; NS — statistically nonsignificant.

	biTLE	uniTLE	p-Value
Number of patients	13	13	
Perinatal insult	4 (30.8%)	3 (23.1%)	NS[a]
Febrile seizures	1 (7.7%)	3 (23.1%)	NS[a]
CNS infection	2 (15.4%)	2 (15.4%)	NS[a]
GTCS < 1 per year	10 (76.9%)	10 (76.9%)	NS[a]
Experience of aura	11 (84.6%)	11 (84.6%)	NS[a]
TSF in median [min–max]	7 [1–25]	7 [1–12]	NS[b]

[a] Fisher's exact test.
[b] Mann–Whitney test.

3. Results

3.1. Demographic data

The study included a total of 26 patients: 13 fulfilled the criteria for the group with biTLE and 13 fulfilled the criteria for the group with uniTLE. In the group with biTLE, there were 7 females and 6 males, and the age at the evaluation ranged from 19 to 51 years (with an average of 34 ± 9.8 years). In the group with uniTLE, there were 4 females and 9 males, and the age at the evaluation ranged from 21 to 47 years (with an average of 35 ± 8.2 years). The data regarding patient characteristics are summarized in Table 1.

3.1.1. Presurgical evaluation — language dominance

In 24 patients, left-sided language dominance was proven according to the Wada test (Table 1). In patients 9 and 15, the Wada test was not performed, but other clinical data and neuropsychological results indicated left-sided dominance.

3.1.2. Surgery, histopathological findings, and outcome

Of the 13 patients in the group with biTLE, eight (61.5%) underwent resective surgery, four (30.8%) received primarily VNS, and one (7.7%) refused VNS implantation. Three patients received VNS after unsuccessful resective surgery. AMTR was performed in seven (87.5%) out of the eight patients who underwent resective surgery; the resection of temporal pole was performed in one (12.5%) patient. In the group with uniTLE, all of the patients underwent resective surgery; AMTR was performed in 11 (84.6%) out of 13 patients, and extended lesionectomy was performed in the remaining two (15.4%) patients. Histopathological findings were available in eight (61.5%) patients in the group with biTLE and in all 13 patients in the group with uniTLE (Table 1). Regarding the outcome in the eight patients from the group with biTLE who underwent resective surgery, two (25%) patients were classed as Engel I (IA and IB), one (12.5%) patient was classed as Engel II (IIA), two (25%) patients were classed as Engel III (both IIIA), and three (37.5%) patients were classed as Engel IV. Seizure outcome in seven patients with biTLE after VNS implantation were classified, using the modified McHugh classification, as the following: I (one patient; 14.3%), II (one patient; 14.3%), III (one patient; 14.3%), and V (four patients; 57.1%). In the group with uniTLE, all of the patients were completely seizure-free after surgery, as defined in the inclusion criteria.

3.2. Differences between the group with biTLE and the group with uniTLE

3.2.1. Anamnestic data

Anamnestic data describing the group with biTLE and the group with uniTLE are summarized in Table 2. No statistically significant differences were found between the group with biTLE and that with uniTLE.

3.2.2. Semi-invasive ictal EEG parameters

A total of 93 seizures were recorded in 26 patients during semi-invasive EEG. A total of 35 seizures were analyzed in the group with biTLE (range = 2–6 per patient; average of 2.69 ± 1.18) and 58 seizures in the group with uniTLE (range = 2–9 per patient; average of 4.46 ± 2.30). Technically acceptable recordings of all evaluated ictal EEG parameters were available in 33 (94.3%) out of 35 seizures in the group with biTLE and in 52 (89.7%) out of 58 seizures in the group with uniTLE. We did not find any significant differences in terms of predefined semi-invasive ictal EEG parameters between the group with biTLE and the group with uniTLE (Table 3).

3.2.3. Seizure semiology

A total of 164 seizures recorded during both semi-invasive EEG and invasive EEG monitoring were included in the seizure semiology analysis. In the group with biTLE, a total of 86 seizures were analyzed (range = 4–13 per patient; average of 6.62 ± 2.66), including 67 CPSs. Similarly, in the group with uniTLE, a total of 78 seizures were analyzed (range = 3–9 per patient; average of 6.00 ± 1.87), including 61 CPSs. At least one IMS was observed in 18 (20.7%) out of 87 seizures in the group with biTLE and in 47 (61.0%) out of 77 seizures in the group with uniTLE ($p < 0.001$). The individual IMS average per seizure was significantly lower in the group with biTLE, with a median of 0.14 (range = 0–1.0) than in the group with uniTLE, with a median of 0.80 (range = 0–2.6) ($p = 0.003$) (Table 4). The distribution of each particular lateralizing sign in both groups is shown in Table 5. Table 5 also provides information about the percentage of lateralizing signs that were concordant with SOZ (in the group with uniTLE) or with the predominant SOZ (in the biTLE group). Postictal unresponsiveness shorter than 3 min was observed in 18 (28.6%) out of 63 seizures in the group with biTLE and in 34 (57.6%) out of 59 seizures in the group with uniTLE. In contrast, PU was longer than 5 min in 27 (42.9%) out of 63 seizures in the group with biTLE and in 11 (18.6%) out of 59 seizures in the group with uniTLE. This different distribution of PU among seizures of both groups reached statistical significance ($p = 0.002$) (Table 6). In the group with biTLE, the invasive part of the evaluation revealed six patients with a predominant SOZ in the left (i.e., language-dominant) hemisphere, six patients with a predominant SOZ in the right (i.e., language nondominant) hemisphere, and one patient with a 1:1 ratio of seizures originating from both hemispheres. In the group with uniTLE, there were seven patients with a SOZ in the left (i.e., language-dominant) hemisphere and six patients with a SOZ in the right (i.e., language nondominant) hemisphere. In the group with biTLE, we analyzed a total of 63 seizures, from which 29 were registered in patients with a predominant SOZ in the left (i.e., language-dominant) side (46.0%) and 34 seizures in patients with a predominant SOZ in the right (i.e., language nondominant) side. In the group with uniTLE, we analyzed a total of 59 seizures, from which 35 were in patients with a predominant SOZ in the left (i.e., language-dominant) side (59.3%) and 24 seizures in patients with a predominant SOZ in the right (i.e., language nondominant) side. Other features of ictal and periictal semiology did not differ significantly between the two groups (Table 4).

Table 3
Characteristics of biTLE and uniTLE semi-invasive ictal EEG data. ERTA — presence of early rhythmic theta/alpha activity; TRTA — time to rhythmic theta/alpha activity; BPT — bitemporal propagation time; IAD — ictal activity duration; NS — statistically nonsignificant.

	biTLE	uniTLE	p-Value
ERTA/number of analyzed seizures	31/34 (91.2%)	52/53 (98.1%)	NS[a]
Individual TRTA average [min–max] (seconds)	8.0 [2.0–60.5]	4.3 [1.0–10.5]	NS[b]
Individual BPT average [min–max] (seconds)	13.5 [1.0–64.5]	10.5 [3.5–30.0]	NS[b]
Individual IAD average [min–max] (seconds)	80.0 [49.0–332.5]	74.5 [26.0–143.0]	NS[b]

[a] Fisher's exact test.
[b] Mann–Whitney test.

Table 4
Comparison of ictal and periictal semiology between the group with biTLE and that with uniTLE. EOAs — early oroalimentary automatisms; IMSs — ictal motor signs; PIVSs — periictal vegetative symptoms; PIMSs — periictal motor signs; NS — statistically nonsignificant.

	biTLE	uniTLE	p-Value
Number of patients/seizures	13/87	13/77	
EOAs in ≥1 seizure	9 (69.2%)	7 (53.8%)	NS[a]
EOAs in seizures	25 (28.7%)	18 (23.4%)	NS[a]
IMSs in ≥1 seizure	6 (46.2%)	12 (92.3%)	$p = 0.030$[a]
≥1 IMS in seizures	18 (20.7%)	47 (61.0%)	$p < 0.001$[a]
Individual IMS average per seizure [min–max]	0.14 [0–1.0]	0.80 [0–2.6]	$p = 0.003$[b]
PIVSs in ≥1 seizure	4 (30.8%)	7 (53.8%)	NS[a]
≥1 PIVS in seizures	13 (14.9%)	14 (18.2%)	NS[a]
PIMSs in ≥1 seizure	11 (91.7%)[c]	11 (84.6%)	NS[a]
≥1 PIMS in seizures	40 (62.5%)	34 (57.6%)	NS[a]

[a] Fisher's exact test.
[b] Mann–Whitney test.
[c] Seizures of patient no. 9 were not analyzed [all registered seizures were secondarily generalized].

Table 5
The distribution of the occurrence among the four ictal motor signs by group and lateralizing value with respect to the predominant side of seizure-onset zone. IMSs — ictal motor signs; SOZ — localization of seizure-onset zone; ENHT — early nonversive head turning; ID — ictal dystonia; LII — lateralized ictal immobility of the upper limb; RINCH — rhythmic ictal nonclonic hand motions. ENHT was considered concordant if it occurred ipsilateral to the predominant SOZ; the other three IMSs (ID, LII, and RINCH) were considered concordant if they occurred contralateral to the predominant SOZ.

	biTLE		uniTLE	
	Total number of seizures where IMSs are present	IMSs concordant with the predominant side of SOZ	Total number of seizures where IMSs are present	IMSs concordant with the side of SOZ
ENHT	5	4/5 (80%)	31	27/31 (87.1%)
ID	1	1/1 (100%)	16	16/16 (100%)
LII	18	15/18 (83.3%)	30	28/30 (93.3%)
RINCH	1	0/1 (0%)	4	4/4 (100%)

Table 6
Postictal responsiveness in the group with biTLE and that with uniTLE. CPSs — complex partial seizures; PU — postictal unresponsiveness; NS — statistically nonsignificant.

	biTLE	uniTLE	p-Value
Number of patients/seizures	12[a]/63	13/59	
PU in all CPSs ≤ 5 min	3 (25.0)	9 (69.2)	$p = 0.047$[b]
PU in all CPSs > 5 min	9 (75.0)	4 (30.8)	
PU < 3 min	18 (28.6)	34 (57.6)	$p = 0.002$[b]
PU 3–5 min	18 (28.6)	14 (23.7)	
PU > 5 min	27 (42.9)	11 (18.6)	

[a] Seizures of patient no. 9 were not analyzed [all registered seizures were secondarily generalized].
[b] Fisher's exact test.

4. Discussion

4.1. Definition of bitemporal epilepsy

Although the existence of independent bitemporal seizure onsets has been clearly demonstrated by invasive EEG recordings, the term "bitemporal epilepsy" differs substantially among published studies and is used in various clinical situations. Bitemporal epilepsy was defined in previous invasive studies as intractable TLE with "at least one independent seizure arising from each temporal lobe" [1,3–5], "predominance of seizure origin <80% in one from both temporal lobes" [19], or was defined by various combinations of criteria (scalp and sphenoidal EEG, MRI findings, and neuropsychological results) independently on invasive EEG results [20]. In other studies, the term "bitemporal epilepsy" was interpreted as clinical seizures arising independently from both temporal lobes in scalp EEG recordings [21] or bilateral independent seizure origin in scalp or invasive EEG recordings [22,23]. As a rule, patients with only interictal bitemporal epileptiform abnormalities were not declared as patients with bitemporal epilepsy [19,24–29]. Our definition of a group with bitemporal epilepsy is similar to that of Hirsch et al. [1], with the exception of the inclusion of patients with habitual complex partial seizures elicited by electrical stimulation.

4.2. Anamnestic data

We did not observe any significant difference between the two groups with respect to epilepsy risk factors. In agreement with a previous study by Hirsch et al. [1], we did not notice any statistical difference between the group with biTLE and the group with uniTLE in terms of TSF, GTCS frequency, or anamnestic experience of aura. We did not evaluate other history data such as age at epilepsy onset, duration of epilepsy, or histopathological findings. These parameters do not differ statistically between bitemporal and unitemporal patients [1], although one study showed an earlier age at epilepsy onset in bitemporal patients [18].

4.3. Semi-invasive EEG ictal parameters

We did not find any significant differences between the group with biTLE and that with uniTLE in terms of predefined EEG variables. The high incidence of ERTA in both the group with biTLE and the group with uniTLE is a typical ictal EEG finding in patients with TLE [30]. Parameters describing time course of seizures (BPT and IAD) were not found to play any role in biTLE identification because both groups varied extremely, both interindividually and intraindividually. This supports the previously observed vast diversity in propagation models [31–35].

4.4. Ictal and postictal semiology

We systematically assessed the semiology of biTLE in comparison with uniTLE. Hirsch et al. [3] did not find significant differences in bitemporal epilepsy when analyzing the clinical uniformity of seizures originating in each temporal lobe. In contrast to some previous comprehensive semiologic studies in TLE [36,37], we analyzed the frequency of separate symptoms (EOAs and PU) as well as the frequency of predefined symptom clusters (IMSs, PIVSs, and PIMSs). The first main difference between the group with biTLE and the group with uniTLE was the lower frequency of IMSs in the course of the seizures in patients from the group with biTLE. The second significant difference was longer PU in the group with biTLE than in the group with uniTLE. One possible reason for the lack of IMSs in the majority of the seizures in the group with biTLE may be a more rapid contralateral seizure spread in biTLE than in uniTLE, which does not permit the evolution of typically lateralized TLE semiology. Although the short contralateral spread may be due to the presence of a more seizure-prone contralateral hippocampus [31], there may also be evidence of specific independent or connected networks in both temporal foci. Our results from scalp and sphenoidal EEG did not directly support these hypotheses. The hypotheses should be tested with a depth electrode study with a detailed analysis of the ictal involvement of the main structures of both temporal lobes, which was impossible in our study.

To the best of our knowledge, the term "postictal unresponsiveness" has not been used and evaluated in CPSs in TLE to clinically describe the altered behavioral state in the meaning of postictal dysphasia and/or confusion. Privitera et al. [38] introduced the Cincinnati method of postictal language assesment, in which postictal confusion does not interfere or rarely interferes with postictal language testing [39]. The

ability to correctly read a test phrase during the first 60 s after the end of ictal EEG activity lateralizes seizure origin to the nondominant hemisphere whether [38] or not it is propagated to the dominant temporal lobe [40]. When multiple task postictal language testing was used previously, there were no significant differences between left-sided seizures and right-sided seizures in the mean interval to the first correct verbal response [41]. The main limitation of multiple task postictal testing is that there is no single task presentation (and, consequently, no clear-cut time of each task presentation). In the present study, we used multiple task testing, but we measured the interval to full recovery of normal contact without impaired speech and without confusion. Late phases of the postictal period were divided into three relatively long periods, with the first cutoff notably long after the sensitive period of the Cincinnati method (i.e., 3 min after the end of the seizure). This difference between the group with biTLE and the group with uniTLE is not caused directly by a different seizure duration (IAD) or by the distribution of the predominant SOZ side among both hemispheres in the group with uniTLE and the group with biTLE. Based on these results, we suppose that the difference in "postictal unresponsiveness" between the two groups was not caused by more seizures arising from the language-dominant side in patients in the group with biTLE, even though invasive recordings of all of the seizures were not used in this part of analysis. Further detailed study is needed. Postictal unresponsiveness longer than 3 min probably indicates temporal lobe seizures with origin or propagation in/to the dominant hemisphere and/or seizures with prolonged postictal confusion. The major proportion of patients and seizures with PU longer than 5 min in the group with biTLE may be explained by hypothetically more profound functional impairment of both temporal lobes in the group with biTLE. One may speculate that the effect of a seizure is more profound in the group with biTLE, because both temporal lobes are seizure-prone.

4.5. Surgery and outcome

In our study, 61.5% of the patients in the group with biTLE underwent resective surgery, which is comparable with the literature. In previous series with invasive EEG, the percentage of evaluated bitemporal patients who had surgery was 43–53% [3,4,21]. Literature data concerning the postoperative outcome in patients with bitemporal epilepsy are difficult to interpret because outcome assessment differs among studies. Published data imply that 75–100% seizure reduction (not including auras) was achieved in 50.0–93.3% of operated patients [3,4,18,21], and completely seizure-free outcome was achieved in 12.5–45.5% of operated patients [3,5,18].

Favorable VNS efficacy in the treatment of bitemporal epilepsy was documented in a proportion of patients as comparable with other epilepsy syndromes [22,42]. Our results of resective surgery and VNS efficacy are limited because of the low patient number. One patient reached seizure freedom; VNS was effective (McHugh I or II) in about one-third of our patients.

5. Conclusions

Our study analyzes differences in seizure semiology between bitemporal TLE and unilateral TLE. We demonstrated a higher frequency of ictal motor signs in patients in the group with uniTLE and longer postictal unresponsiveness in patients in the group with biTLE. The major limitation of this study was the small sample size. Further evaluation on the basis of invasive EEG is needed to confirm the results of our study.

Acknowledgments

We are grateful to Radka Kubíková for work on the Wada test data collection. We thank Anne Johnson for grammatical assistance.

This study was supported by the "CEITEC — Central European Institute of Technology" project (CZ.1.05/1.1.00/02.0068) from the European Regional Development Fund.

Conflict of interest

None of the authors has any conflict of interest to disclose.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Annex 11: Chrastina J, Novak Z, Zeman T, Kocvarova J, Pail M, **Dolezalova I**, Jarkovsky J, Brazdil M. Single-center long-term results of vagus nerve stimulation for epilepsy: A 10-17 year follow-up study. Seizure – European Journal of Epilepsy. 2018;59:41-47.

Seizure 59 (2018) 41–47

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Single-center long-term results of vagus nerve stimulation for epilepsy: A 10–17 year follow-up study

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ARTICLE INFO

Article history:
Received 27 January 2018
Received in revised form 12 March 2018
Accepted 26 April 2018

Keywords:
Epilepsy
Vagus nerve stimulation
Long term follow up
Responder
Battery replacement

ABSTRACT

Purpose: The paper presents a long-term follow-up study of VNS patients, analyzing seizure outcome, medication changes, and surgical problems.
Method: 74 adults with VNS for 10 to 17 years were evaluated yearly as: non-responder – NR (seizure frequency reduction <50%), responder – R (reduction ≥ 50% and <90%), and 90% responder – 90R (reduction ≥ 90%). Delayed R or 90R (≥ 4 years after surgery), patients with antiepileptic medication changes and battery or complete system replacement were identified. Statistical analysis of potential outcome predictors (age, seizure duration, MRI, seizure type) was performed.
Results: The rates of R and 90R related to the patients with outcome data available for the study years 1, 2, 10, and 17 were for R 38.4%, 51.4%, 63.6%, and 77.8%, and for 90R 1.4%, 5.6%, 15.1%, and 11.1%. The absolute numbers of R and 90R increased until years 2 and 6. Antiepileptic therapy was changed in 62 patients (87.9%). There were 11 delayed R and four delayed 90R, with medication changes in the majority. At least one battery replacement was performed in 51 patients (68.9%), 49 of whom R or 90R. VNS system was completely replaced in 7 patients (9.5%) and explanted in 7 NR (9.5%). No significant predictor of VNS outcome was found.
Conclusions: After an initial increase, the rate of R and 90R remains stable in long-term follow-up. The changes of antiepileptic treatment in most patients potentially influence the outcome. Battery replacements or malfunctioning system exchange reflect the patient's satisfaction and correlate with good outcomes.

1. Introduction

Since the first implantation in humans in 1988 and Food and Drug Administration (FDA) approval in 1997, vagus nerve stimulation (VNS) has become an accepted palliative treatment modality for patients with drug-resistant epilepsy not suitable for resective surgery. The effect of VNS on seizure frequency and severity was confirmed by randomized controlled trials [1,2,3,4]. However the follow-up period in the first three studies did not exceed 26 weeks [1,2,3]. The last paper, a metanalysis of 74 studies with 3321 enrolled patients, proved a significant reduction of seizures at 3–12 months after surgery (36%) and an increasing effect of VNS on seizure reduction at >1year after surgery [4]. Other studies confirm a cumulative effect of VNS in medium-duration follow-up. For example, the median seizure reduction in 454 patients enrolled in five double-blind US studies improved from 35% to 44% at two years [5]. Similarly, a European study confirmed that treatment duration was significantly correlated with the percentage of seizure frequency reduction [6]. With increased experience, studies reporting post-VNS outcomes for up to 5 years [7,8] and studies covering follow-up periods exceeding 10–11 years have been published [9,10,11,12]. The effect of VNS on seizure reduction has been discussed in combination with other aspects of VNS: post-VNS quality of life [12] and surgical problems [9].

Abbreviations: FDA, food and drug administration; VNS, vagus nerve stimulation; ILAE, international league against epilepsy; MRI, magnetic resonance imaging; NR, non-responder; R, responder; 90R, 90% responder; DBS, deep brain stimulation.

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https://doi.org/10.1016/j.seizure.2018.04.022
1059-1311/

The first aim of the study is to present the results of VNS systems implanted for ≥ 10 years in patients with drug-resistant epilepsy followed in a specialized epilepsy center in a longitudinal time axis. The effect of VNS on seizure reduction is quantified yearly in terms of responder rates for the entire study period from stimulation onset to study completion. There were marked developments in the field of antiepileptic drugs during the study period. In terms of new medications during the study period (January 2000–November 2017), the date of levetiracetam registration was 29 Sept 2000, for zonisamide 10 Mar 2005 and for pregabalin 6 July 2004. The impact of medication changes during the follow-up period on seizure outcome is also studied, particularly in patients with late or delayed VNS response.

The satisfaction with VNS treatment can be quantified by sophisticated scales evaluating the different aspects of the quality of life [13], but a simple criterion – the frequency of battery replacement after depletion (indicating the patient's or the physician's will to continue VNS therapy in mutual agreement) – can provide a simplified answer. Moreover, surgical problems with the implanted system require revision and replacement and the rate of patients willing to undergo the surgery to continue the VNS therapy during the prolonged follow-up period also provide data about patient satisfaction with the results. Therefore the second aim of the study is the analysis of surgical problems of long-term VNS, with attention to reoperations and system complications in the long-term follow-up period, for which there are only a few comparable papers [10,12]. Finally statistical analysis of potential long- term VNS outcome predictors was performed; unfortunately there are currently no universally accepted outcome predictors for VNS. However, based on previously published papers aiming to find VNS outcome predictors, age, seizure duration, age at seizure onset, MRI findings (diffuse, focal, mesiotemporal sclerosis and negative) and the prevailing seizure type (complex partial seizure – focal aware – ILAE 2017, simple partial seizure – focal impaired awareness – ILAE 2017, and other), were selected as potential predictors for statistical analysis [4,14–16].

2. Material and methods

Adult patients (age ≥ 18 years) with VNS systems (Cyberonics, Inc., Houston, Texas, USA) implanted at the author's department for ≥ 10 years ago were retrospectively identified from a prospectively constructed database of the patients who had surgery for drug-resistant epilepsy at the comprehensive Brno Epilepsy Center. Prior to VNS implantation, all patients underwent a detailed preoperative investigation at the center and were ruled out as suitable candidates for resective epilepsy surgery. After standard implantation of the left vagus nerve stimulation system (ZN, JC), all the patients were followed at the First Department of Neurology at regular intervals (2, 4, 6, 12 and 18 months; then yearly). VNS parameter adjustments and modifications of antiepileptic medication were made strictly according to the clinical decision of the epileptologist.

Based on post-VNS seizure reduction, the patients were graded at the follow-up visits as non-responders – NR (seizure frequency reduction <50%), responders – R (reduction ≥ 50% and <90%), or 90% responders – 90R (reduction ≥ 90%). When the VNS system was switched off due to a response that was not clinically relevant, the patient was moved to the "stimulation off" category and remained there until the end of the follow-up period; other patients were categorized as having had system explantation ("explantation"), as lost to follow-up care ("patient lost"), or as having died for any reason ("dead"). Missing data for a single follow-up visit moved the patient to the "data missing" category for that particular follow-up point. Patients with late response to VNS (shifting from the NR category to the R category, or from the R to the 90R category at ≥ 4 years after surgery), as well as patients with fluctuating or worsening response to VNS during the follow-up period, were identified. The percentages of R, 90R, and Good outcomes (R + 90R) for each study year were related to all the patients with follow-up results available for the defined study year (excluding patients categorized as "dead", "data missing", or "lost").

The medical reports of late responders were checked for medication changes during the year prior to the improved response. The percentage of patients with medication changes (including permanent dosage changes) during the follow-up period was also calculated.

Patients with battery replacement during the follow-up period were identified from the database and confirmed from surgical reports. Similarly, patients requiring complete VNS system replacement (including the helical electrode) were identified, and the cause of system failure was determined from the surgical report. The rates of 90R and Good outcomes were selected as the endpoints of the statistical analysis. The time points for analysis were defined at year 10 and final follow up. Absolute and relative frequencies were accepted for the description of endpoints occurrence. Logistic regression was used for the analysis of relation between predictors and endpoints; odds ratios, their 95% confidence intervals and statistical significance were used for the description of this relationship.

3. Results

The study included 74 adult patients (33 males, 41 females) who had VNS implanted between January 2000 and November 2007. The mean patient age at implantation was 31.1 years (range 18–59 years; standard deviation 10.65 years). There was a history of previous neurosurgical operations in 20 patients (simple lesionectomies in six patients, failed extratemporal or temporal resections in four patients, stereotactic lesional surgeries in seven patients, stereoelectroencephalography not providing adequate data for resective surgery in three patients). Two patients had brain hypothermia. The first case was a 35-year-old male with seizure onset at the age of 2 years (frontal absences with secondary generalization). Hypothermic treatment was administered at the age of 17 years, but without effect on seizure frequency or severity. MRI showed gliotic changes after ventricular punctures. Because the investigations failed to localize the epileptogenic focus, the patient had VNS system implanted, and was categorized as a Responder. The second patient (a 37-year-old male) was treated at another department for multifocal epileptic seizures by stereotactic surgeries (coagulation of the right Forel field, rostral cingulum, and right thalamic nuclei) and with brain hypothermia. After VNS, he was graded as 90R.

Six patients were lost to follow-up before study year 10 (one 90R and five R at the last follow-up). Two patients died before study year 10 (one NR suffered a severe brain injury after epileptic seizure and one NR due to malignant retroperitoneal tumor). The outcome data at the year 10 follow-up visits were available for 66 patients.

Follow-up data of patients with VNS implanted for 17 years were available for nine patients (two patients were lost to follow up; one patient died from neurodegenerative disease).

During the whole study period, there were 8 patients lost to follow-up care (one 90R and 7 R at the last follow-up). Five patients died during the follow-up period. In three patients, the cause of death was unrelated to epilepsy (retroperitoneal malignancy, urinary bladder cancer, and neurodegenerative disease). In one patient, the death was related to epilepsy: a fatal brain injury caused by a fall during an epileptic seizure. The possibility of SUDEP could not be excluded in one patient who reportedly died from heart failure.

Table 1
VNS outcomes – years 1–9.

Study Year	1	2	3	4	5	6	7	8	9
NR	44	30	28	21	16	11	10	9	6
R	28	37	37	36	36	37	38	38	41
90R	1	4	7	10	12	13	11	12	10
Stimulation Off	0	0	1	2	3	3	4	4	6
Explantation	0	1	1	1	3	4	4	4	4
Patient Lost	0	0	0	2	3	5	5	6	6
Dead	0	0	0	0	0	1	1	1	1
Data Missing	1	2	0	2	1	0	1	0	0
Together	74	74	74	74	74	74	74	74	74
Good results (R + 90R)	29	41	44	46	48	50	49	50	51
Bad results (NR+ Stimulation Off + Explantation)	44	31	30	24	22	18	18	17	16
R rate (%)	38.4	51.4	50.0	51.4	51.4	54.4	56.7	56.7	61.2
90R rate (%)	1.4	5.6	9.5	14.3	17.1	19.1	16.4	17.8	14.7
R + 90R rate (%)	39.8	57.0	59.5	65.7	68.5	73.5	73.1	74.5	75.9

General overviews of the results are presented in Table 1 (follow-up years 1–9) and Table 2 (follow-up years 10–17) and Graphs 1 and 2.

The rates of R, 90R and Good outcomes can be related to the complete group of patients (including patients with no available data because they were lost to follow-up, dead, or had data missing). This calculation underestimates the percentage of good results, because it in fact presumes that all patients with unavailable results had bad outcomes. The second possibility is that the rates of R, 90R, and Good outcomes are related to the patients with available follow-up data. This calculation overestimates the percentage of good results when the data unavailability is caused by the dropout of patients who are not doing well. Seven of the patients who were lost to follow-up were categorized as R and one as 90R before their loss. Of the five patients who died during the study period, two patients were graded before their death as 90R, one as R, and two as NR. Three of the patients categorized as "data missing" at a certain follow-up point were graded as NR at the next follow-up; two of them finally reached R grading. The other two patients categorized as "data missing" at a certain visit were evaluated as R and 90R at the next follow-up. Because good results were documented in the vast majority of the patients who were lost to follow-up care, dead, or had data missing, the rates of R and 90R were related to the group of patients with follow-up data available (excluding "lost", "dead", or "data missing"); in author's opinion, this minimizes the distortion of results. The probable reason that patients with good outcomes dropped out was their choice to continue follow-up care in their native country or closer to their home (our center was the first in the country to start systematic VNS implantation).

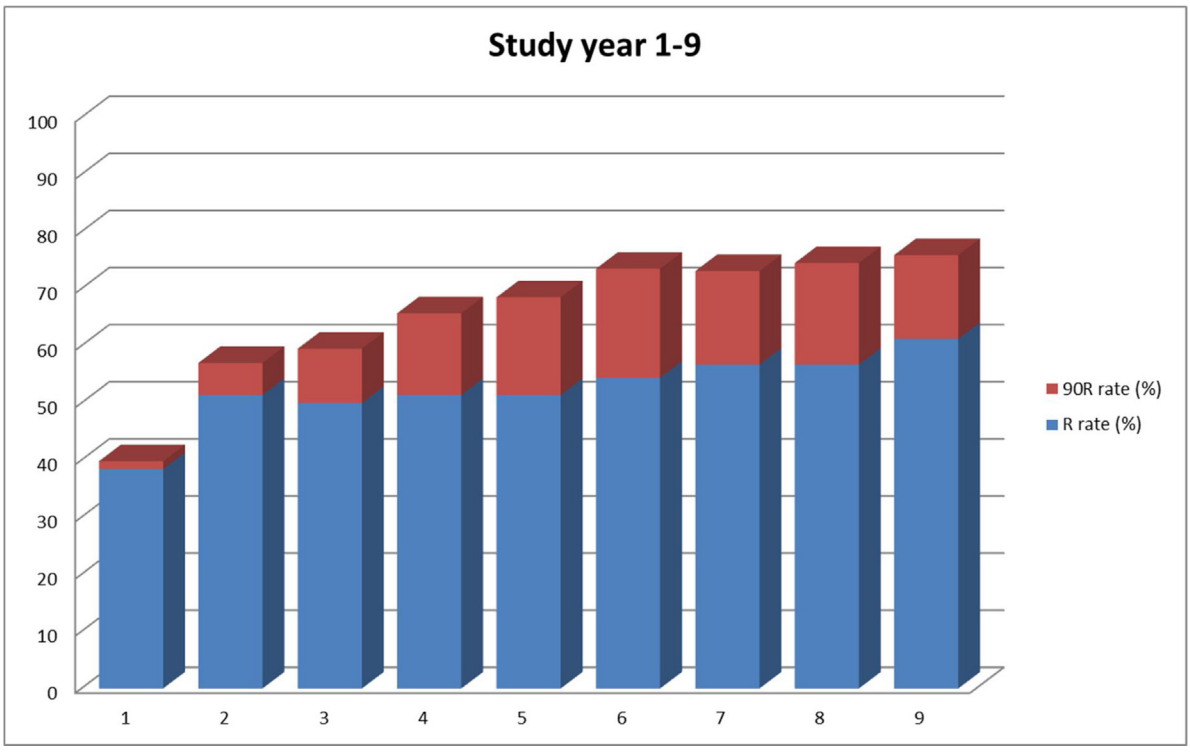
From the 28 patients evaluated as VNS responders at the one-year follow-up visit, the number of responders increased to 37 at the two-year follow-up visit and remained stable with minimal fluctuations (36–42) until study year 10. The number of 90R increased until study year 6. This trend is also reflected in the dynamics of Good outcomes (R + 90R): the peak number was reached at study year 6 and then remained stable with minimal fluctuations (49–52). The nearly steady number of R from study year 2 can be explained by the dynamic equilibrium of patient inflow from the NR to R category together with the outflow from R to 90R and by the dropout of Responders. The 90R rate increases from 1.4% at year 1 to 19.1% at study year 6, then slightly decreases due to the dropout of two 90R patients reaching 15.4% at study year 10. The R and Good outcome rates increase from 38.4% and 39.8% at study year 1, to 51.4% and 57.0% for study year 2, and to 63.1% and 78.7% at study year 10.

Because the number of study patients decreased during years 10 to 17, only the rates of R, 90R and Good outcomes were analyzed. The 90R rates fluctuate between 11.1% (study year 17; only 9 patients available for analysis) and 20% (study year 15). The R rate remains relatively stable between years 10 and 16 (56.1% to 63.1%) with an R rate of 77.8% at study year 17. The Good outcomes rate varies between 70.8% and 81.8% for study years 10–16 and reaches 88.9% for study year 17.

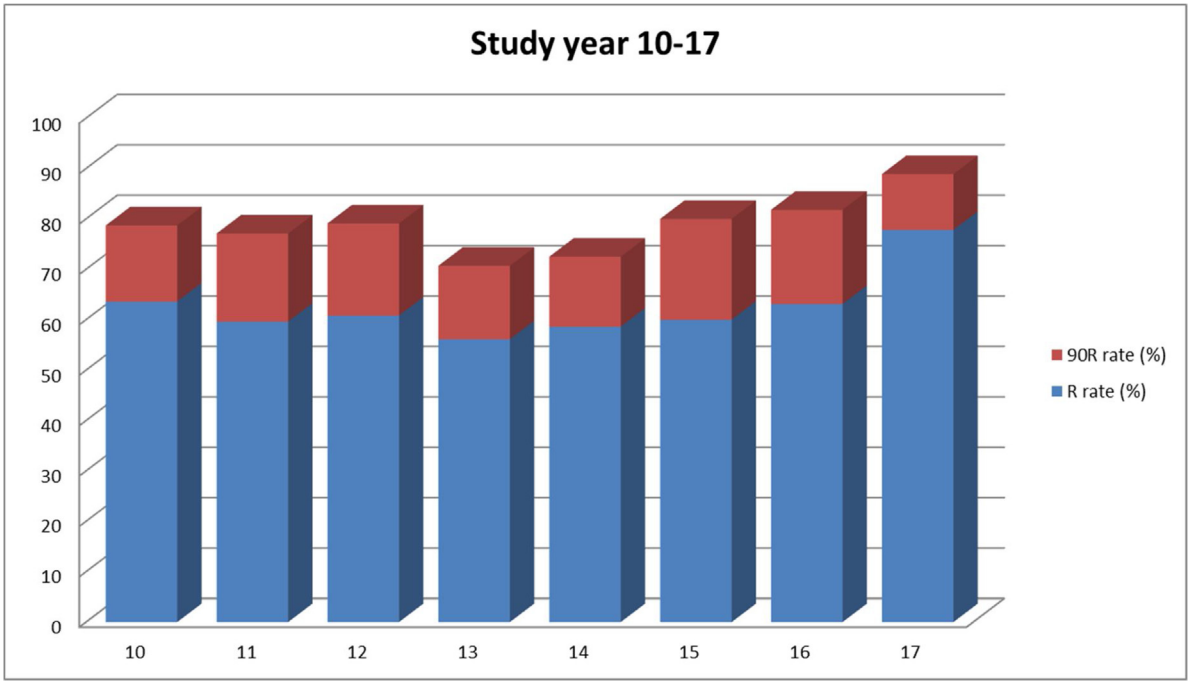
Twelve patients were graded as 90R at their final follow-up visit (including one patient lost to subsequent follow-up care and one patient who died of neurodegenerative disease). A seizure-free period lasting at least one year prior to the final follow-up was achieved in two patients (one patient had a 13 year-seizure-free period after three years evaluated as NR; one patient was 9 years seizure free after a one-year follow-up evaluation as NR).

Table 2
VNS outcomes – years 10–17.

Study year	10	11	12	13	14	15	16	17
NR	3	3	1	1	0	0	0	0
R	42	34	28	23	17	15	10	7
90R	10	10	9	6	4	5	3	1
Stimulation Off	6	5	4	4	3	1	1	0
Explantation	5	5	7	7	5	4	2	1
Patient Lost	6	3	3	3	3	2	2	2
Dead	2	2	2	4	4	4	2	1
Data Missing	0	0	0	0	0	0	0	0
Together	74	62	54	48	36	31	20	12
Good results (R + 90R)	52	44	37	29	21	20	13	8
Bad results (NR+ Stimulation Off + Explantation)	14	13	12	12	8	5	3	1
R rate (%)	63.6	59.6	60.8	56.1	58.6	60.0	63.1	77.8
90R rate (%)	15.1	17.5	18.3	14.6	13.9	20.0	18.7	11.1
R + 90R rate (%)	78.7	77.1	75.5	70.7	72.5	80.0	81.8	88.9



Graph 1. The dynamics of R and 90R rate in time – study years 1–9.



Graph 2. The dynamics of R and 90R rate in time – study years 10–17.

During the study period, previously switched off VNS systems were explanted in seven NR patients because of further evaluation for resective surgery, deep brain stimulation (DBS), or at the patient's request. The system was completely removed in six patients. In one patient the battery was removed for cosmetic reasons and the helical electrodes around the nerve were intentionally left at the patient's request.

Antiepileptic therapy remained unchanged during the study period in nine patients (12.1%).

11 patients (14.8%) achieved an R grade not earlier than at the year 4 follow-up visit. During the last year before their favorable response, there were medication changes in nine of them (Table 3); six had increased their medication dose. Four patients improved from R to 90R not earlier than at the year 4 follow-up visit. Three of

Table 3
VNS patients with delayed R rate.

Patient number	Year of significant response	Medication change	Type of change
1	4	no change	no change
2	8	yes	increased lacosamide dose
3	4	yes	increased topiramate dose
4	6	yes	increased zonisamide dose
5	4	no change	no change
6	7	yes	increased levetiracetam dose
7	4	yes	stopped levetiracetam, started lamotrigine
8	6	yes	increased pregabalin dose
9	10	yes	clonazepam added
10	4	yes	stopped primidone, started topiramate
11	4	yes	increased levetiracetam dose

Table 4
VNS patients with delayed 90R rate.

Patient number	Year of 90R	Grading before 90R	Medication change	Type of medication change
1	4	R	no change	no change
2	4	R	yes	carbamazepine dose reduction, increase of VNS stimulation
3	4	R	yes	stopped pregabalin, started clonazepam
4	5	R	yes	added clonazepam and lamotrigine

them had changes in antiepileptic treatment in the previous year (Table 4).

Three patients with fluctuating response to VNS were identified. One patient was initially graded as R; at the years 3 and 4 visits, she deteriorated to the NR category, but during all the following visits she was graded as R. Another patient was graded as R during the entire follow-up period except for at the years 5 and 6 follow-up visits, where she was graded as NR. One patient with a fluctuating response deteriorated to NR after the year 5 follow-up visit (R year 1, NR years 2 and 3, R years 4 and 5, NR after year 5).

During the study period, one or more battery replacements were performed due to the depleted battery in 51 patients (68.9%). At the time of battery replacement, 49 patients (66.2%) were graded as R or 90R. Battery replacement was also indicated in two NR patients; the seizure reduction rate was 30–40% in both with positive effects from extrastimulation. In 11 patients, the battery was replaced twice; in one patient, it was replaced three times. A complete system replacement was necessary for seven patients (categorized as R before system problems) (9.5%); in one of them, the entire system had to be replaced twice. In all patients, the indication for system replacement was excessive system impedance with decreasing stimulation efficacy. During surgical revision, only fibrosis around the helical electrodes and nerve was found in all patients. There was no case of electrode violation or helical electrode dislocation.

Further surgeries in NR patients were performed after VNS system explantation; these included DBS (bilateral anterior thalamic nucleus) in two patients and resective surgeries in two patients (anteromedial temporal resection initially refused by the patient and frontal topectomy after stereoelectroencephalography). In all the patients operated on after VNS explantation, the results of postexplantation MRI did not differ from the preVNS findings. Among the remaining nonresponders who underwent VNS explantation, there was no case with a resectable lesion detected even using high field MRI.

The rate of VNS system infection and wound breakdown was 0%. There was one case of seroma and another case of hematoma around the battery, both conservatively treated without further consequences.

Among the parameters potentially predicting long term VNS outcome no significant predictor of VNS outcomes as measured by the frequencies of endpoints (90R and Good outcomes) was found using the selected statistical methodology.

4. Discussion

The presented study has a long follow-up period, lasting from 10 to 17 years. The results confirm that the benefit to patients with VNS from systematic treatment in a specialized epilepsy center increases over time. When comparing our results with a long-term study by Wasade et al. [12] with 207 patients, the overall results regarding seizure control are comparable (>50% seizure reduction in 68% of patients) with the exception of higher seizure freedom rates in the Wasade study (20%). In the Wasade study, 22 patients were surveyed from a group of 36 patients with VNS durations of 10 to 14 years (13 with favorable outcomes), and 11 patients were surveyed from a group of 24 patients with follow-up care lasting over 15 years (seven favorable outcomes). Our study had a higher rate of patients available for analysis.

The steady rise of good outcome rates (R + 90R) after study year 2 together with the percentage of patients with late response to VNS (>4 years postimplantation) support prolonging the waiting period before evaluating VNS as ineffective. The adequate duration of this period is unclear [8]. Salinsky et al. [17] suggested that patient response during the first three months could foretell subsequent treatment effectiveness. However, Schachter et al. [18] encouraged continuing VNS for up to two years before discontinuation due to inefficacy. A long-term increase in VNS responder rates was supported by the extensive multicenter study published by Kuba et al. [19] with responder rates of 44.4% at one year after stimulation was initiated increasing to 58.7% after two years and 64.4% at five years. In a paper by Uthman et al. [20], the decrease of seizure frequency was 26% after one year, 30% after five years, and 52% after 12 years of VNS. Ryzí et al. [21] assessed long-term seizure outcomes in a group of 15 children with the mean seizure reduction of 42.5% at one year, 54.9% at two years, and 58.3% at five years. The responder rates remained stable at study year 2, at 60%, and at study year 5, at 60%. Serdaroglu et al. [11] confirmed that, once achieved, positive VNS results are stable or improve over time. In our study, only one patient deteriorated to NR after five years of follow-up observation with a fluctuating response. Despite

the difficult calculations of the R rate and 90R rate considering the drop of patients, the results are comparable with the literature data both for study period years 1–10 and years 11–17.

During the study period, antiepileptic treatment was changed in 87.9% and remained unchanged in 12.1% of patients. The high percentage of patients with antiepileptic medication changes was undoubtedly related to the boom in this field. In a paper by Arcand et al. [22], the percentages of VNS patients with medication changes in type or dose during follow-up care were 57% at 6 months, 33% at 12 months, 59% at 24 months, and 81% at 36 months (mainly dose increases). The percentage of responders did not match the increased number of patients with medication changes – 43% at 6 months, 48% at 12 months, 41% at 24 months, and 50% at 36 months. A detailed analysis proved that maximum improvements correlated with the time of changed medication. These results correlate with our findings about medication changes in patients with late VNS response: in the year prior to the delayed VNS response improvement, there was an antiepileptic drug dose increase in 54.5% and a medication change in 27.2% of delayed responders. Medication was changed in 50% of the delayed 90R patients. Not all papers confirm the positive role of medication adjustments in VNS outcome. In a paper by García-Pallero et al. [23], the percentage of responders in the group with no medication changes allowed was 63%; in the comparable group of patients with medication changes permitted, 45.2% were responders. According to the authors, the absence of changes in antiepileptic drugs helps to optimize the stimulation parameters.

The most frequent reason for revision surgery of the VNS system in our group was battery replacement due to battery depletion. In a study of 1234 patients, Lam et al. [24] reported the average incidence of revision surgeries within six years of follow-up care as <1% for electrode revision, <3% for battery revision or removal, 4–10% for battery replacement, and <1% for infection washout, confirming the highest frequency for battery replacements during a shorter follow-up period. In a study by Couch et al. [25] describing 1144 VNS procedures, 46% of patients required at least one battery replacement or revision surgery, mostly for battery depletion (27%), poor seizure control efficacy (9%), lead malfunction (8%), and infection (2%). In our patients, the indications for battery replacement were decreasing or depleted battery capacity. Attention should be paid to the timing of system revision or battery replacement. According to Vonck et al. [26], pre-replacement seizure control could not be regained in 2 of 14 patients with replacement postponed for several months. Similarly, Tatum et al. [27] support battery replacement before the end of battery life because of the symptoms preceding the end of battery life, such as seizure and behavioral worsening. In our study, no case was observed of the loss of the pre-replacement seizure control after battery depletion and replacement.

The indication for system replacement in our study was increased system impedance with the clinical correlation of seizure worsening; there were no cases of infection or system violation. During surgery, fibrosis around the nerve portion with helical electrodes was found in all patients. No case of electrode displacement was observed. The 9.5% incidence of complete system replacement correlates with literature data reporting the incidence of device malfunction at 4–16.8% of implanted systems [28].

Apart from standard surgical problems of battery or complete system replacement, other aspects of VNS revision surgeries should be discussed. The effect of VNS therapy may be measured by seizure reduction, but also by patient satisfaction and the impact of VNS on the patient's quality of life. For example, Ryvlin et al. [13] proved that VNS therapy as a treatment adjunct to best medical practices in patients with pharmacoresistant focal seizures was associated with a significant improvement in health-related quality of life compared with best medical practices alone. In addition to sophisticated scales, the willingness of the patient (or the physician) to continue therapy by means of undergoing a relatively simple surgery (battery replacement) or a more difficult intervention, such as complete VNS system replacement, may be considered an indicator of treatment success. Based on this simple criterion, the VNS success rate is 78.5% (battery replacement rate 68.9% and complete system replacement 9.5%). This figure correlates with a study reporting that 80% of the surveyed patients considered the VNS worthwhile [12].

Although the incidence of infection was 0%, the increasing risk of implant complications during the prolonged follow-up treatment cannot be excluded despite the smaller battery and cable size as compared to currently available DBS hardware. This assumption is supported by a study of 247 VNS patients with a mean follow-up period of 12 years, in which the incidence of complications was 8.6%, including postoperative hematoma (1.9%) and infection (2.6%) [10].

5. Conclusions

The paper provides an exceptionally long-term follow-up view of VNS patients, involving seizure outcome and other factors. Long-term follow-up results indicate that vagus nerve stimulation is a safe and effective palliative treatment option for drug-resistant epilepsy and its efficacy does not decrease with time. After an initial steady increase until year 6 the number of patients with good VNS outcomes (R + 90R) remained stable. Changes in antiepileptic treatment took place during the entire follow-up period in 87.9% of patients, with potential impacts on seizure reduction. In most patients with delayed response to VNS the improved seizure control was preceded by a change in antiepileptic treatment during the previous year. Patient's age, seizure duration, age at seizure onset, MRI findings and the prevailing seizure type are not significant predictor of long term VNS outcomes.The patient's or treating physician's satisfaction and willingness to continue VNS treatment is indicated by the rate of depleted battery replacement and complete system replacement and corresponds with the rate of good VNS outcomes. In terms of surgical complications in this long-term follow-up study, VNS proved to be a safe technique with a very low rate of transient treatable problems.

Conflict of interest

The authors have no conflict of interest to declare.

Acknowledgements

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for- profit sectors

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Annex 12: Chrastina J, Kocvarova J, Novak Z, **Dolezalova I**, Svoboda M, Brazdil M. Older age and longer epilepsy duration do not predict worse seizure reduction outcome after vagus nerve stimulation. Journal of neurological surgery part A – Central European neurosurgery. 2018;79(2):152-158.

Older Age and Longer Epilepsy Duration Do Not Predict Worse Seizure Reduction Outcome after Vagus Nerve Stimulation

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Abstract

Introduction We analyzed the results of vagus nerve stimulation (VNS) on older patients and patients with long-lasting epilepsy and included severely intellectually disabled patients.

Patients and Methods A total of 103 adults with VNS implanted from 2005 to 2014 were studied. The responder rates, that is, the percentage of VNS patients who responded to VNS, classified as seizure reduction $\geq$ 50% (50R) and seizure reduction $\geq$ 90% (90R), were compared in defined age groups ($<$ 40 and $\geq$ 40 years, and $<$ 50 and $\geq$ 50 years) and epilepsy duration groups ($<$ 20 and $\geq$ 20 years, $<$ 30 and $\geq$ 30 years, and $<$ 40 and $\geq$ 40 years) at the 1-year follow-up visit and the last follow-up visit (at least 2 years after surgery). The age distributions and responder rates were also studied in patients with an intellectual disability.

Results The analysis did not confirm a significantly lower 50R or 90R rate in patients $\geq$ 40, $\geq$ 50, or $\geq$ 60 years when compared with their younger counterparts, but the 50R rate increase during follow-up care was the lowest in patients $\geq$ 50 and $\geq$ 60 years. The highest percentage of patients with an intellectual disability in the group $<$ 40 years of age did not adversely affect the 50R rate. Longer epilepsy duration was not confirmed as a negative predictor of VNS outcome. There was a significantly higher 50R rate in patients with epilepsy duration $\geq$ 20 years (at the last follow-up visit) and a higher 90R rate in patients with epilepsy duration $\geq$ 30 years (at the 1-year follow-up visit). The increase in the 50R rate during follow-up care was lower in patients with epilepsy durations $\geq$ 30 and $\geq$ 40 years.

Conclusions The study did not find worse VNS outcomes, as defined by the 50R or 90R rate, in older adult patients or in patients with a longer epilepsy duration. The increasing stimulation effect over time is less marked in older patients and in patients with longer epilepsy duration.

Keywords
- epilepsy
- vagus nerve stimulation
- seizures reduction
- responder

received
January 9, 2017
accepted after revision
August 2, 2017

DOI https://doi.org/10.1055/s-0037-1607396.
ISSN 2193-6315.

Introduction

Vagus nerve stimulation (VNS) is a safe and effective palliative surgical treatment for refractory epilepsy not amenable to resection. The effect of VNS on seizure frequency and severity was confirmed by three randomized controlled trials.[1–3] In general, a > 50% seizure reduction can be expected in at least 50% of patients after 2 years of treatment with mild side effects.[4,5] The effect of stimulation is not immediate, but it increases over time after device implantation.[6] The U.S. Food and Drug Administration (FDA) approved VNS in 1997 as an adjunctive therapy for intractable partial epilepsy in patients ≥ 12 years of age who are ineligible for resection; the indications for VNS are even wider including generalized epilepsies,[7] Lennox-Gastaut syndrome,[8] and very young children with epilepsy.[9,10]

Complete freedom from seizures is rarely achieved using VNS, and 25% of patients had no benefit.[3] The standard evaluation scales (Engel and International League Against Epilepsy) are not suitable for VNS outcome studies. The percentage of seizure reduction and the frequency of responders (patients with a seizure reduction of at least 50% from baseline) are usually reported.

Because of the progress in epilepsy surgery and the general awareness of surgical results and safety, older patients with chronic or lifetime intractable seizures as well as patients with an intellectual disability with the aim of seizure palliation and easier caregiving are more frequently referred for surgery. VNS implantation is not a difficult surgery and has few complications; it is therefore an attractive option for such patients. However, secondary epileptogenesis after long-lasting multiple seizures with a progressive course of the epileptic disorder, potentially leading to unsatisfactory treatment results, must be considered.[11] Brain injuries caused by falls during seizures and possible cerebrovascular accidents in middle-aged and older patients may also negatively influence the VNS outcome. Although the impact of mental disability on VNS outcome is not clear,[12,13] its negative role cannot be excluded.

This article presents the results of VNS in older patients and patients with longer epilepsy duration with the potential implication for VNS indication in older patients with long-term epilepsy. The secondary aim was to analyze the potential impact on VNS outcomes with the inclusion of patients with severe intellectual disabilities.

Patients and Methods

A total of 103 patients (47 men and 56 women, all > 18 years) with refractory epilepsy not suitable for resection had VNS system implantation from 2005 to 2014. The patients referred had multiple seizure types: complex partial seizure, complex partial seizure (CPS) with generalization, primarily generalized seizure, generalized tonic-clonic seizure (GTCS), simple partial seizure, and simple partial seizure with generalization. All of the patients underwent a complete presurgical evaluation at the Brno Epilepsy Center including video electroencephalogram (EEG) monitoring with interictal and ictal recordings, special epilepsy magnetic resonance imaging (MRI) protocol, and neuropsychology and functional imaging (single-photon emission computed tomography [SPECT], positron emission tomography, subtraction ictal SPECT coregistered with MRI) performed according to clinical needs. Before VNS, four patients underwent resective surgery without invasive exploration (one extratemporal and three temporal resections; two for a low-grade tumor), and callosotomy was performed in two patients, all with unsatisfactory control of seizures. Invasive EEG was required in 12 patients and failed to identify a resectable epileptogenic focus in 6 patients. In the remaining six patients, the results of stereoelectroencephalography allowed resective surgery but without a worthwhile reduction of seizures.

VNS implantation was performed by one of two neurosurgeons (Z.N. or J.C.). The only surgical complication was transient hoarseness in four patients.

After implantation, the patients were followed at the First Department of Neurology at regular intervals (2, 4, 6, and 12 months; then yearly). Stimulation adjustments and antiepileptic treatment changes were made by the responsible physician.

The study data were obtained retrospectively from medical records. Based on post-VNS seizure reduction, the patient was graded as a nonresponder (NR) (seizure frequency reduction < 50%), 50R (seizure frequency reduction ≥ 50%), or 90R (seizure frequency reduction ≥ 90%).

The percentage of 50R and 90R rates was compared between patients < 40 years and ≥ 40 years and between patients aged < 50 years and ≥ 50 years of age at the 1-year follow-up visit and the last follow-up visit (at least 2 years after surgery, maximum 10 years, median 5 years). There were 65 patients < 40 years, 27 patients ≥ 40 years but < 50 years, 11 patients ≥ 50 years, and 5 patients ≥ 60 years.

The percentage of patients with severe intellectual disabilities (unable to take care of themselves, requiring institutional care) was 9.1% in patients ≥ 50 years (1 patient), 17.4% in patients < 50 years (16 patients), 7.9% in patients ≥ 40 years (3 patients), and 21.5% in patients < 40 years (14 patients). The causes of severe intellectual impairments were perinatal problems (most patients), meningoencephalitis, extensive developmental anomaly of the brain, tuberous sclerosis, and idiopathic.

The effect of epilepsy duration on seizure outcome was analyzed by comparing 50R and 90R rates between patients with epilepsy duration < 20 years and ≥ 20 years, < 30 years and ≥ 30 years, and < 40 years and ≥ 40 years at the 1-year follow-up visit and the last follow-up visit. There were 38 patients with epilepsy duration < 20 years and 64 patients with epilepsy duration ≥ 20 years, 64 patients with epilepsy duration < 30 years and 38 patients with epilepsy duration ≥ 30 years, 84 patients with epilepsy duration < 40 years and 18 with epilepsy duration ≥ 40 years, and 6 patients with epilepsy duration ≥ 50 years. One patient with an uncertain epilepsy duration (the data from the patient and the patient's medical records differed) was excluded from the analysis.

Continuous parameters were described using medians (5% and 95%) and were tested using the Mann-Whitney test. Categorical parameters were described by absolute (relative) incidence, and the Fisher exact test was used. The analysis was supported by prediction of 50R and 90R at the 1-year follow-up visit and the last follow-up visit using logistic regression with age at implantation and seizure duration for the whole group.

Results

The outcomes were available for 103 patients at the 1-year follow-up visit and for 94 patients at the last follow-up visit. During the study period, the VNS system was explanted in seven NRs; two of them underwent palliative resection (both Engel III), and anterior thalamic nucleus stimulation was used in three patients.

►**Table 1** summarizes the first part of the results, 50R rates at the 1-year follow-up visit and the last follow-up visit in the defined age and epilepsy duration categories.

The statistical analysis did not prove a significant adverse effect of age on 50R rates for the age thresholds of 40 and 50 years. On the contrary, 50R rates were nonsignificantly higher in patients $\geq$ 40 years both at the 1-year follow-up and the last follow-up visit and in patients $\geq$ 50 years at the 1-year follow-up visit only. In the small group of five patients $\geq$ 60 years, the 50R rate was 60% at the 1-year follow-up visit and the last follow-up visit.

However, instead of the expected increase in the 50R rate over time between the 1-year follow-up visit and the last follow-up visit, there was a decrease of the 50R rate in the patients $\geq$ 50 years of age (−3.7%). However, this decreased 50R rate in the group of 11 patients $\geq$ 50 years (7/11 [63.7%] to 6/10 [60%]) was caused by one patient (50R at the 1-year follow-up visit) who was lost to follow-up care for the final control. When removing this patient from the calculations, the 50R rate in patients $\geq$ 50 years at the 1-year and the last follow-up visits remained stable at 60% because all other 50Rs remained in this category.

The adverse effect of longer epilepsy duration on 50R rates has not been proven for all the analyzed epilepsy duration thresholds. On the contrary, a significantly higher 50R rate was found in patients with epilepsy duration $\geq$ 20 years at the last follow-up visit. Moreover, the median duration of epilepsy in 50R is significantly higher than in NRs (28.5 years and 20.0 years, respectively; $p = 0.029$). However, the increase in 50R rate during follow-up care is lower in patients with longer epilepsy duration: patients $<$ 30 years 17.1%, $>$ 30 years 2%, patients $<$ 40 years 13.7%, and $>$ 40 years 1.4%. In six patients with epilepsy duration $\geq$ 50 years, the 50R rate was 50% at both follow-up visits.

►**Table 2** summarizes the 90R rates in the defined age and epilepsy duration categories at the 1-year follow-up and last follow-up visits. No significant difference was found in 90R rates between the 1-year and last follow-up visits in all age groups. Surprisingly, there was a significantly higher 90R rate in patients with epilepsy duration $\geq$ 30 years at the first follow-up visit ($p = 0.026$). The difference between the median duration of epilepsy in 90Rs (32.5 years) and the rest of the group (24.0 years) does not reach statistical significance ($p = 0.058$). An increase in the percentage of 90Rs during follow-up care is observed in all age and epilepsy duration groups, although this finding is definitively weakened by the small number of 90Rs.

The results of VNS in terms of 50R and 90R in intellectually disabled patients are summarized in ►**Table 3**. The median

Table 1 Effect of age and epilepsy duration on percentage of vagus nerve stimulation $\geq$ 50% seizure reduction at 1-year and final follow-up visits

	50R 1-year follow-up		*p* value	50R Final follow-up		*p* value
	No	Yes		No	Yes	
Age, y (range)	33.0 (20.0–54.0)	35.0 (19.0–61.0)	0.594	31.0 (20.0–60.0)	34.0 (19.0–58.0)	0.417
$<$ 40 (%)	32 (49.2)	33 (50.8)	0.542	23 (38.3)	37 (61.7)	0.501
$\geq$ 40 (%)	16 (42.1)	22 (57.9)		10 (29.4)	24 (70.6)	
$<$ 50 (%)	44 (47.8)	48 (52.2)	0.537	29 (34.5)	55 (65.5)	0.737
$\geq$ 50 (%)	4 (36.4)	7 (63.6)		4 (40.0)	6 (60.0)	
Epilepsy duration, y (range)	22.0 (5.0–54.0)	28.5 (9.0–50.0)	**0.029**	18.0 (4.0–54.0)	26.5 (8.0–48.5)	0.120
$<$ 20 (%)	22 (57.9)	16 (42.1)	0.104	18 (48.6)	19 (51.4)	**0.046**
$\geq$ 20 (%)	26 (40.6)	38 (59.4)		15 (26.8)	41 (73.2)	
$<$ 30 (%)	35 (54.7)	29 (45.3)	0.064	22 (37.3)	37 (62.7)	0.660
$\geq$ 30 (%)	13 (34.2)	25 (65.8)		11 (32.4)	23 (67.6)	
$<$ 40 (%)	41 (48.8)	43 (51.2)	0.604	27 (35.1)	50 (64.9)	0.999
$\geq$ 40 (%)	7 (38.9)	11 (61.1)		6 (37.5)	10 (62.5)	

Abbreviation: 50R, $\geq$ 50% seizure reduction.

Table 2 Effect of age and epilepsy duration on percentage of vagus nerve stimulation ≥ 90% seizure reduction at 1-year and final follow-up visits

	90R 1-year follow-up		*p* value	90R Final follow-up		*p* value
	No	Yes		No	Yes	
Age, y (range)	34.0 (20.0–58.0)	37.0 (20.0–61.0)	0.525	33.0 (20.0–60.0)	37.0 (19.0–50.0)	0.759
< 40 (%)	60 (92.3)	5 (7.7)	0.999	53 (88.3)	7 (11.7)	0.743
≥ 40 (%)	36 (94.7)	2 (5.3)		31 (91.2)	3 (8.8)	
< 50 (%)	86 (93.5)	6 (6.5)	0.558	75 (89.3)	9 (10.7)	0.999
≥ 50 (%)	10 (90.9)	1 (9.1)		9 (90.0)	1 (10.0)	
Epilepsy duration, y (range)	24.0 (5.0–50.0)	32.5 (21.0–61.0)	0.058	24.0 (5.0–54.0)	32.0 (18.0–44.0)	0.117
< 20 (%)	38 (100.0)	0 (0.0)	0.082	36 (97.3)	1 (2.7)	0.081
≥ 20 (%)	58 (90.6)	6 (9.4)		48 (85.7)	8 (14.3)	
< 30 (%)	63 (98.4)	1 (1.6)	**0.026**	56 (94.9)	3 (5.1)	0.069
≥ 30 (%)	33 (86.8)	5 (13.2)		28 (82.4)	6 (17.6)	
< 40 (%)	80 (95.2)	4 (4.8)	0,285	70 (90.9)	7 (9.1)	0.650
≥ 40 (%)	16 (88.9)	2 (11.1)		14 (87.5)	2 (12.5)	

Abbreviation: 90R, ≥ 90% seizure reduction.

age in the disabled patient group was significantly lower than in the group of patients without an intellectual disability (25.0 years and 34.0 years, respectively). Although the difference does not reach the level of statistical significance, the rates of 50R at both the 1-year follow-up and last follow-up visit were higher in the intellectually disabled patients. Therefore, the higher percentage of these patients in the younger age group does not adversely affect the percentage of 50R rates in younger patients.

The results of the logistic regression for the entire group with age at implantation and epilepsy duration for prediction of 50R and 90R for 1-year and last follow-up visits are summarized in ►**Tables 4–7**. This analysis confirmed only longer epilepsy duration as a predictor of a higher percentage of 50R at the 1-year follow-up visit (odds ratio: 1.067; 95% confidence interval, 1.011–1.127; $p = 0.019$), but this predictive value of longer epilepsy duration was lost at the last follow-up visit. Higher age was not confirmed as a negative predictive factor.

The changes of seizure pattern and severity were inconsistent in all the studied age and seizure duration groups, for example, frequency reduction without change of seizure severity, lesser clustering or cumulation, shorter seizure duration, reduction or elimination of falls, marked reduction of CPS with stable or minimally reduced frequency of GTCS or marked reduction of GTCS with stable frequency of CPS. Thus no statistical analysis was possible.

Discussion

Despite new antiepileptic drugs and advances in epilepsy surgery, a significant number of patients remain unresponsive to both pharmacotherapy and resective surgery. VNS, a safe and adjustable technique reducing the frequency and severity of intractable seizures with few adverse effects, is an attractive option. Although multiple factors potentially influencing VNS outcome have been studied (e.g., age, epilepsy duration, frequency, semiology, etiology, interictal EEG, and radiologic findings),[3,14,15] the effect of VNS cannot be predicted reliably. Even the studies analyzing easily definable factors, such as age and epilepsy duration, produced contradictory results. Part of the difficulty in defining the best patient population may be the poor understanding of VNS action mechanisms. Moreover, single-center VNS series do not usually include homogeneous patient populations in terms of rare epileptic syndromes[16] or even in terms of age and epilepsy duration (e.g., middle-aged and older patients, patients with long-lasting seizures).

The problem with the inclusion of intellectually disabled patients is that the percentage of them is substantially higher in younger age groups as confirmed by their median age being significantly lower than that of the intellectually unaffected patients included in the study. One possible explanation is that there is still some reluctance to refer older institutionalized patients with an intellectual disability and chronic seizures for surgical treatment. But the higher percentage of intellectually disabled patients in the younger age group did not adversely affect the rate of 50R in younger patients.

Most articles analyzing the impact of patient age at implantation on seizure reduction have dealt with children and young adolescents. Lagae et al showed that age at VNS implantation is the only factor predicting seizure outcome in childhood epilepsy with particularly favorable results in children < 5 years.[17] The

Table 3 Intellectually disabled patients: characteristics and vagus nerve stimulation outcomes

	Intellectual disability		*p* value
	No	Yes	
Age, y (range)	34.0 (20.0–60.0)	25.0 (18.0–50.0)	**0.024**
< 40 (%)	53 (60.2)	14 (82.4)	0.102
≥ 40 (%)	35 (39.8)	3 (17.6)	
< 50 (%)	78 (88.6)	16 (94.1)	0.688
≥ 50 (%)	10 (11.4)	1 (5.9)	
Epilepsy duration (range)	24.0 (5.0–54.0)	24.0 (16.0–50.0)	0.712
< 20	35 (40.2)	5 (29.4)	0.587
≥ 20 (%)	52 (59.8)	12 (70.6)	
< 30 (%)	54 (62.1)	12 (70.6)	0.590
≥ 30 (%)	33 (37.9)	5 (29.4)	
< 40 (%)	71 (81.6)	15 (88.2)	0.730
≥ 40 (%)	16 (18.4)	2 (11.8)	
50 R, 1-year follow-up			
No (%)	42 (48.3)	6 (37.5)	0.587
Yes (%)	45 (51.7)	10 (62.5)	
50R, final follow-up			
No (%)	30 (37.5)	3 (21.4)	0.365
Yes (%)	50 (62.5)	11 (78.6)	
90R, 1-year follow-up			
No (%)	80 (92.0)	16 (100.0)	0,592
Yes (%)	7 (8.0)	0 (0.0)	
90R, final follow-up			
No (%)	71 (88.8)	13 (92.9)	0.999
Yes (%)	9 (11.3)	1 (7.1)	

Abbreviation: 50R, ≥ 50% seizure reduction; 90R, ≥ 90% seizure reduction.

Table 4 Prediction of ≥ 50% seizure reduction, logistic regression with age at implantation and seizure duration, at the 1-year follow-up visit

	OR	95% CI	*p* value
Age	0.952	0.894–1.014	0.128
Epilepsy duration	1.067	1.011–1.127	**0.019**

Abbreviations: CI, confidence interval; OR, odds ratio.

Table 5 Prediction of ≥ 50% seizure reduction, logistic regression with age at implantation and seizure duration, at final follow-up visit

	OR	95% CI	*p* value
Age	0.986	0.927–1.049	0.659
Epilepsy duration	1.031	0.976–1.089	0.274

Abbreviations: CI, confidence interval; OR, odds ratio.

Table 6 Prediction of ≥ 90% seizure reduction, logistic regression with age at implantation and seizure duration, at the 1-year follow-up visit

	OR	95% CI	*p* value
Age	0.916	0.757–1.107	0.362
Epilepsy duration	1.140	0.954–1.362	0.149

Abbreviations: CI, confidence interval; OR, odds ratio.

Table 7 Prediction of ≥ 90% seizure reduction, logistic regression with age at implantation and seizure duration, at final follow-up visit

	OR	95% CI	*p* value
Age	0.937	0.821–1.070	0.338
Epilepsy duration	1.084	0.959–1.226	0.195

Abbreviations: CI, confidence interval; OR, odds ratio.

potential explanation of better results in younger patients from pediatric groups may be the higher threshold for excitatory stimuli and seizure-induced changes in immature brains than in adult brains (based on an experimental study of amygdaloid kindling in a cat model).[18] Alexopoulos et al found that age < 12 years at implantation (FDA-defined threshold) is actually associated with a better prognosis when considering median seizure frequency reduction.[19] Similarly, Meng et al showed a higher percentage of 50R in patients < 12 years (71.4%) than in their older counterparts (60.6%).[20] For different age thresholds, Wheless and Maggio found better VNS results in patients < 18 years.[21]

However, other reports do not confirm a better VNS outcome in younger patients. Thompson et al showed no significant differences in seizure frequency reduction, epilepsy duration, overall clinical improvement, or improvement in quality of life based on age < 12 or ≥ 12 years.[22] In a Czech multicenter study, lower efficacy rates of VNS in patients < 16 years were observed.[23] An Israeli retrospective multicenter open-label study comparing seizure reduction in patients < 22 and ≥ 22 years found higher 50R rates in older patients.[24] Wheeler et al studied seizure outcome in age categories 0 to 20 years, 21 to 40 years, and > 40 years at VNS implantation. The percentage of patients with at least a worthwhile reduction of seizures (Engel I, II, and III) was 51% for 0 to 20 years, 69% for 21 to 40 years, and 80% for patients > 40 years. The outcomes in patients > 50 years were comparable. However, significantly higher percentages of Engel I and II were found in patients with better mental functioning; this finding does not agree with our results.[25] A multicenter study of 45 adults > 50 years found that their response to VNS was similar to that of younger adults without increased morbidity.[26]

Our data do not confirm a statistically significant negative impact of age (for age thresholds 40 and 50 years using the Mann-Whitney test, and for the whole group using logistic regression) on VNS 50R rates. Statistically nonsignificant 50R rates were actually higher in patients ≥ 40 years at both the 1-year and the last follow-up visits and in patients ≥ 50 years at the 1-year follow-up visit. An increased VNS effect, as defined by an increasing 50R rate, was not observed in patients ≥ 50 and ≥ 60 years.

The rate of 90R in the selected age categories was also comparable. This finding matches the data presented by Englott et al, who observed no relationship between the age at implantation and seizure freedom rate.[27] Our results do not confirm higher age to be a negative predictor of VNS effect.

Another study aim was to analyze the effect of VNS in patients with long-lasting epilepsy. The expected worse outcomes in patients with long-lasting epilepsy were supported by some literature results. An analysis of the Cyberonics VNS patient registry data found a significantly higher percentages of patients with 100% seizure reduction and $\geq 90\%$ seizure reduction in patients with VNS within 6 years of seizure onset.[28] According to Englott et al, there is a trend among patients with shorter epilepsy duration (threshold 10 years) before VNS for a higher frequency of seizure freedom.[27] Although the short 3-month follow-up care is a serious limitation in a study by Ranfroe and Wheless, the percentage of seizure-free patients after VNS with epilepsy duration < 5 years was 15%, and 4.4% in patients with epilepsy duration > 5 years.[29]

However, the association of longer epilepsy duration with worse outcomes was not confirmed by other studies. In a two-center study (Belgium and the United States), the percentage of Engel I to III outcomes was 61% in patients with epilepsy duration < 10 years and 70% in patients with epilepsy duration ≥ 10 years, but this difference was not statistically significant.[25] Lagae et al did not confirm epilepsy duration as a prognostic factor in children and young adults.[17] In a study of patients with extremely variable epilepsy durations (from 3 months to 57 years), Colicchio et al stated that longer epilepsy duration has a positive effect on seizure outcome.[30] Our results do not confirm an adverse effect of epilepsy duration on the rate of 50R. On the contrary, the median duration of epilepsy in 50Rs is significantly higher than in NRs, and a significantly higher percentage of 50R was found in patients with epilepsy duration ≥ 30 years at the last follow-up visit. However, the increase in 50R rates during follow-up care is lower in patients with longer epilepsy duration. This correlates with the results of a logistic regression that confirmed longer epilepsy duration as a predictor of a higher percentage of 50R at the 1-year follow-up visit but not at the last follow-up visit.

Because the mechanism of action of VNS is still largely unknown, it is difficult to provide an undisputable explanation for the less marked increase of 50R rates comparing the 1-year follow-up and last follow-up visits in older patients and patients with prolonged epilepsy duration. The research into the mechanisms of action of various strategies for electrical modulation of the brain suggests a crucial role of different neurotransmitter molecules and channels, such as glutamate, γ-aminobutyric acid (GABA), adenosine, brain-derived neurotrophic factors, and calcium and sodium channels. Electrical modulation of the brain might also promote neurogenesis in subjects with pharmacoresistant epilepsy in whom this process is decreased.[31] Walker et al demonstrated in an animal model that an increase in GABA transmission or a decrease in glutamate transmission reduces susceptibility to limbic motor seizures.[32] Also, recent preclinical experiments indicate that activation of the noradrenergic system in the locus coeruleus (the primary site of vagal afferent termination) is critical for the antiepileptic effect of VNS.[33] Therefore, the hypothetically reduced potential for the process of neurogenesis and decreased synthesis of neurotransmitters in older patients or patients exhausted by long-lasting epilepsy provide a potential explanation for the lower increase of responder rates during follow-up care.

Conclusions

Older age and prolonged duration of epilepsy were not confirmed as negative predictors of VNS outcome as evaluated by the percentage of 50R and 90R at the 1-year and last follow-up visit, with even significantly higher 50R rates in

patients with epilepsy duration $\geq$ 20 years at the last follow-up visit. The highest percentage of intellectually disabled patients in patients $<$ 40 years did not adversely influence the 50R rate in this group. However, there are less prominent increases in VNS effect over time, as evaluated by 50R and 90R rates, in older patients and in patients with longer histories of epilepsy.

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frontiers in Neurology

ORIGINAL RESEARCH
published: 02 May 2019
doi: 10.3389/fneur.2019.00392

EEG Reactivity Predicts Individual Efficacy of Vagal Nerve Stimulation in Intractable Epileptics

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OPEN ACCESS

Edited by:
Fernando Cendes, Campinas State University, Brazil

Reviewed by:
Francesco Marrosu, University of Cagliari, Italy
Roger Walz, Federal University of Santa Catarina, Brazil

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Specialty section:
This article was submitted to Epilepsy, a section of the journal Frontiers in Neurology

Received: *09 December 2018*
Accepted: *01 April 2019*
Published: *02 May 2019*

Citation:
Brázdil M, Doležalová I, Koritáková E, Chládek J, Roman R, Pail M, Jurák P, Shaw DJ and Chrastina J (2019) EEG Reactivity Predicts Individual Efficacy of Vagal Nerve Stimulation in Intractable Epileptics. Front. Neurol. 10:392. doi: 10.3389/fneur.2019.00392

Background: Chronic vagal nerve stimulation (VNS) is a well-established non-pharmacological treatment option for drug-resistant epilepsy. This study sought to develop a statistical model for prediction of VNS efficacy. We hypothesized that reactivity of the electroencephalogram (EEG) to external stimuli measured during routine preoperative evaluation differs between VNS responders and non-responders.

Materials and Methods: Power spectral analyses were computed retrospectively on pre-operative EEG recordings from 60 epileptic patients with VNS. Thirty five responders and 25 non-responders were compared on the relative power values in four standard frequency bands and eight conditions of clinical assessment—eyes opening/closing, photic stimulation, and hyperventilation. Using logistic regression, groups of electrodes within anatomical areas identified as maximally discriminative by *n* leave-one-out iterations were used to classify patients. The reliability of the predictive model was verified with an independent data-set from 22 additional patients.

Results: Power spectral analyses revealed significant differences in EEG reactivity between responders and non-responders; specifically, the dynamics of alpha and gamma activity strongly reflected VNS efficacy. Using individual EEG reactivity to develop and validate a predictive model, we discriminated between responders and non-responders with 86% accuracy, 83% sensitivity, and 90% specificity.

Conclusion: We present a new statistical model with which EEG reactivity to external stimuli during routine presurgical evaluation can be seen as a promising avenue for the identification of patients with favorable VNS outcome. This novel method for the prediction of VNS efficacy might represent a breakthrough in the management of drug-resistant epilepsy, with wide-reaching medical and economic implications.

Keywords: vagal nerve stimulation, neurostimulation, epilepsy, efficacy prediction, EEG reactivity, epilepsy treatment

INTRODUCTION

Resective surgery is currently the best therapeutic option for treatment of patients with drug-resistant epilepsy, but a substantial number of intractable patients remains who are ineligible for such treatment or for whom resective surgery fails to abolish seizures. Chronic vagal nerve stimulation (VNS) has become a well-established alternative, offering a palliative method of treatment for drug-resistant epilepsy; it rarely results in complete seizure freedom (∼5% of treated patients), but provides substantial (≥50%) seizure reduction in 50–60% of individuals. Unfortunately, however, seizure frequency remains unchanged after VNS therapy in ∼25% of patients (1, 2).

Identifying individuals who will benefit from VNS therapy prior to the implantation of the VNS device would improve patient selection, minimize unnecessary surgical procedures, and reduce associated financial expenses dramatically; and yet there exists no method with which to predict individual efficacy pre-intervention (2). Achieving a pre-operative classification of individual patients as VNS responders or non-responders (i.e., patients with ≥50% or <50% seizure reduction, respectively) would represent a major breakthrough in the treatment of drug-resistant epilepsy.

It is presumed that VNS increases seizure threshold by activating neuronal networks in the thalamus and other limbic structures (3, 4), but the precise mechanism of VNS action is not yet understood fully. Both synchronization and desynchronization of the electroencephalogram (EEG) has been proposed as a possible mechanism behind the antiepileptic effect of VNS (5, 6), and recent neurophysiological studies focusing on EEG parameters lend support to this: Fraschini et al. report a significant correlation between VNS-induced global desynchronization in gamma bands and positive clinical outcome in temporal lobe epilepsy patients (7). Similarly, Bodin et al. revealed a lower level of global EEG synchronization in delta and alpha frequency bands during the ON phase of VNS in responders (8). Theoretically, differential alterations in brain rhythms from VNS therapy between responders and non-responders might reflect inter-individual variability in the (non-specific) susceptibility of EEG to be synchronized or desynchronized by external stimulation. It follows that differences in this susceptibility might underlie individual VNS efficacy.

We tested the hypothesis that EEG reactivity to standard external stimuli used during routine pre-operative EEG assessment differs between VNS responders and non-responders, with the aim of developing a reliable statistical model for prediction of VNS efficacy.

MATERIALS AND METHODS

Study Design

We performed retrospective analyses of EEG data collected from all adult patients implanted with a VNS device for drug-resistant epilepsy in the Brno Epilepsy Center between 2005 and 2015. Data from patients implanted between 2005 and 2012 were used for investigation of EEG reactivity to external stimuli and subsequently for development of the statistical model **(Cohort 1).** Additional data from patients implanted with VNS between 2013 and 2015 were used as independent data-set for validation of the statistical model **(Cohort 2).** All the data were acquired during routine outpatient pre-operative assessment, 20 min recording at morning with two standard eyes opening and closing activation procedures (i.e., 10 s period with eyes open), photic stimulation (PS), and hyperventilation (HV). Each EEG recording was filtered into individual frequency bands and segmented into specific intervals representing the eyes opening and closing, PS and HV periods. The relative powers of EEG spectrum in distinct time intervals for a particular frequency band and brain area were then calculated.

Based on their individual responses to VNS, patients were categorized as Responders or Non-responders. In Cohort 1, Responders and Non-responders were first compared on the relative power values, and then a statistical model for prediction of VNS efficacy was developed. Subsequently, the validity of the statistical model was tested in Cohort 2. The study was conducted in St. Anne's University Hospital and approved by the local ethics committee. All patients gave their informed written consent for the use of their pre-operative data.

Patients' Description

All patients were implanted with a VNS system (Cyberonics, Houston) according to a standard implantation procedure (9). Before implantation, all patients underwent a comprehensive assessment protocol for epilepsy surgery candidates, including a detailed history and neurological examination, magnetic resonance imaging (MRI), interictal PET, neuropsychological testing, and scalp video-EEG monitoring. In some patients, ictal and interictal SPECT (SISCOM) and invasive video-EEG monitoring have been completed if necessary. Based on the results of all the investigations, patients indicated for VNS and included in this study were ruled out as suitable candidates for resective epilepsy surgery. Our analyses were applied to data acquired from patients who fulfilled the following criteria: The duration of VNS treatment was at least 2 years; the efficacy of VNS treatment was determined in regular visits every 3 or 6 months; and artifact-free pre-operative interictal EEG was available for eye opening and closing, PS and HV periods.

Demographic information and data regarding the type and number of antiepileptic drugs (AEDs) at the time of implantation were obtained by review of patients' charts. The efficacy of VNS was categorized using a classification system reported by McHugh (10). The cut-off value for seizure-reduction between responders and non-responders was 50%. Patients were defined as Responders or Non-responder only if they were categorized as such for the entire follow-up period.

EEG Analysis

First, we compared relative EEG powers between Responders and Non-responders in Cohort 1. Interictal scalp EEG was recorded on a 64-channel Alien Deymed system with international 10–20 electrode placement and a sampling frequency of 128 Hz. Standard antialiasing filters were applied before digitalization. Occasional artifacts were rejected manually and further

processing was performed with artifact-free EEG periods. The resulting EEG signals were filtered into four frequency bands: theta (4–7.5 Hz), alpha (8–12 Hz), beta (14–30 Hz), and gamma (31–45 Hz). A Hilbert transform was then used to estimate the envelopes of pre-defined pass-band frequency oscillations as a function of time (**Figure 1**). The EEG records were segmented into the following conditions (time intervals):

1 –Rest#1 (2 min)
2 –Eyes opening/closing (10 s)
3 –Rest#2 (immediately after eye closure; 10 s)
4 –Photic stimulation (PS; 2.5 min)
5 –Hyperventilation (HV; 4 min)
6 –Eyes opening/closing (10 s)
7 –Rest#3 (immediately after eye closure; 10 s)
8 –Rest#4 (2 min)

Further analysis was focused on oscillatory power changes in these conditions. Absolute mean power of the EEG spectrum was computed as a mean value of the passband power envelope inside each interval separately, for each scalp electrode. Subsequently, relative mean power (RPW) was calculated as a percentage decrease or increase of mean power relative to baseline, i.e., event-related desynchronization or synchronization, respectively. As a baseline we selected Rest#1 (11). We then evaluated differences between Responders and Non-responders by comparing relative power in seven conditions of clinical assessment: Open/Close#1, Rest#2, PS, HV, Open/Close#2, Rest#3, and Rest#4.

Statistical Analysis

Demographic data were compared between Responders and Non-responders using Fisher's exact test or the Mann-Whitney test. Statistical comparisons of RPW between Responders and Non-responders were also performed with Mann-Whitney tests. Using false discovery rate (FDR) (12), p-values for all electrodes were corrected for multiple comparisons in each time interval separately. Differences were considered significant when $p \leq 0.05$.

Prediction of Response to VNS

Developing the Statistical Model

The statistical model for prediction of VNS efficacy was developed from data obtained in Cohort 1 in the following steps: Firstly, electrodes were grouped into seven anatomical regions as follows: (1) left frontal—Fp1, F3, Fz; (2) right frontal—Fp2, F4, Fz; (3) left anterotemporal—F7, T3; (4) right anterotemporal—F8, T4; (5) central—C3, Cz, C4; (6) left posterior quadrant—P3, Pz, T5, O1; (7) right posterior quadrant—P4, Pz, T6, O2. Specifically, mean values were calculated for the respective groups of electrodes. This resulted

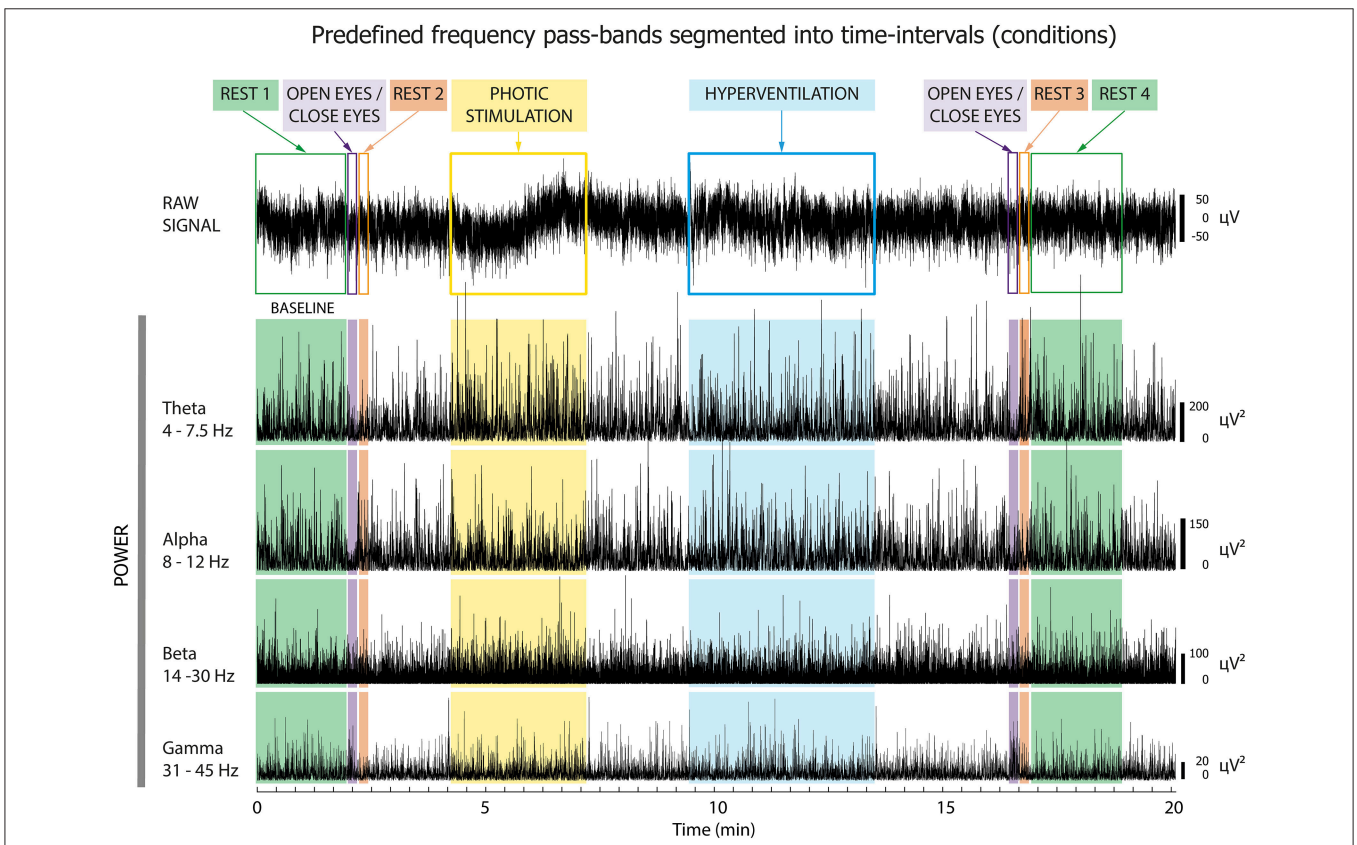

FIGURE 1 | Pre-processing of EEG signal. The EEG was segmented into eight time intervals, and then filtered into four frequency bands: theta, alpha, beta, and gamma. Subsequent analyses focused on the oscillatory power changes within these intervals, which were analyzed separately for each frequency band.

in 196 electrode group variables (7 conditions × 4 frequency bands × 7 anatomical regions). In the second step, the maximally discriminative electrode group variables were then selected using stepwise logistic regression performed in leave-one-out (LOO) manner; specifically, with *n* patients, logistic regression was performed over *n* iterations, each with one subject omitted. This approach allowed us to avoid overestimating the classification results, which occurs when classification is performed on electrode groups selected using all subjects simultaneously. Thirdly, electrode group variables identified most frequently as maximally discriminative after the *n* LOO iterations were used for classification using three classifiers; namely, logistic regression (LR), linear support vector machines (SVM), and linear discriminant analysis (LDA). In this step, we used a LOO cross-validation to split the data into training and testing sets: one patient was chosen randomly as a testing subject and the remaining patients were employed for training the classifier. The testing subject was then classified as belonging to the Responder or to the Non-responder class, and the resulting class label was compared with the true classification label. This procedure was repeated using each of the subjects as the testing subject sequentially, and the overall classification performance measures of accuracy, sensitivity, and specificity were calculated (see the black schematics in **Figure 2**). Fourth, using one-sample binomial test we performed a comparison of the achieved classification accuracies with a classification by chance. We also attempted to predict VNS efficacy based on 532 possible single electrode variables (7 conditions × 4 frequency bands × 19 electrodes; see **Supplementary Material 1**).

Validation of the Statistical Model

The validity of the aforementioned statistical model was verified on the independent data-set obtained from Cohort 2. This validation cohort consisted of patients suffering from drug-resistant epilepsy who were implanted with VNS in our Center between 2013 and 2015. We obtained EEG data recorded using an identical EEG system and pre-surgical assessment protocol, and processed mathematically in the exact same way described above. Patients were classified as Responders and Non-responders with our statistical model using two approaches (see the gray schematics in **Figure 2**). Both began with data reduction, whereby we selected only data corresponding to the maximally discriminative electrode group variables identified based on Cohort 1. In the first approach, this data reduction was followed subsequently by a classification of *m* subjects from Cohort 2 as Responders or Non-responders based on a single classifier, which was trained on all *n* subjects from the Cohort 1. In contrast, in the second approach we classified the reduced data of Cohort 2 using majority voting of *n* classifiers trained on *n*-1 subsets of Cohort 1. The resulting indices for accuracy, sensitivity, and specificity were then compared to those from the classification of Cohort 1.

RESULTS

Participants

Cohort 1

The VNS device was implanted in 110 patients in our center between 2005 and 2012. We excluded 50 patients (45%) from further analyses—17 (15%) because of poor-quality pre-surgical

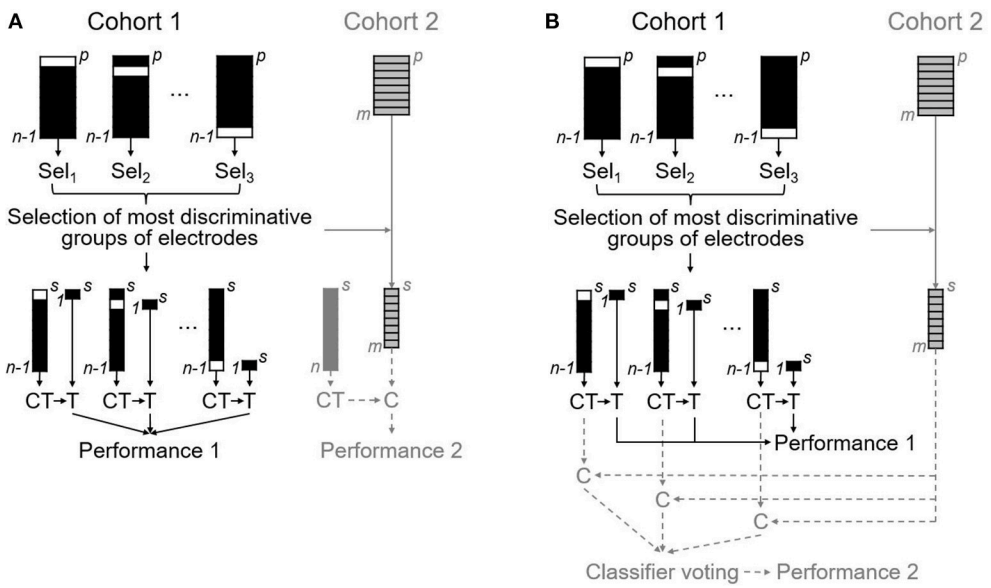

FIGURE 2 | The statistical model for prediction of VNS efficacy based on EEG analysis. Schematics representing the development of the statistical model on data from Cohort 1 outlining the selection of the most discriminative electrodes groups as well as classifier training (CT) and testing (T) performed in LOO manner (the black schematics); and two approaches taken for the validation procedure, whereby our statistical model was applied to an independent data-set from Cohort 2 (the gray schematics). Equivalent steps taken in each of the two validation approaches are visualized using solid lines, including the reduction of Cohort 2 by selecting the maximally discriminative electrodes identified in Cohort 1. The two approaches differ in the steps represented by dashed lines—i.e., the classification (C) of the reduced dataset using: **(A)** a single classifier trained on all *n* subjects from Cohort 1, and **(B)** voting of *n* classifiers trained on *n*-1 subsets of Cohort 1.

EEG, 13 (12%) due to attrition, and 20 (18%) who switched between VNS outcomes during the follow-up period (see **Supplementary Material 2** for details). Demographics for the 60 patients included in the analyses are summarized in **Table 1**. According to the response to VNS, patients were subdivided into 35 (58%) Responders and 25 (42%) Non-responders. When examining demographic data, we observed significant differences between Responders and Non-responders in patients' age at epilepsy onset, duration of epilepsy before VNS implantation, and treatment by valproic acid (**Table 1**).

Cohort 2

In total, the VNS device was implanted in 25 patients between 2013 and 2015. Three patients were excluded from our analyses due to poor-quality pre-surgical EEG recordings. Data from the remaining 22 patients were used for independent validation: 12 (54.5%) Responders and 10 (45.5%) Non-responders. The demographic data are summarized in **Table 1**. The Cohort 2 did not differ from the Cohort 1 in the demographic characteristics, apart from the anticipated difference in duration of VNS ($p < 0.001$) and subtle differences in antiepileptic treatment (specifically, eslicarbazepine, lacosamide, and zonisamide were more frequent in Cohort 2; $p = 0.029$, $p = 0.003$, and $p = 0.012$, respectively).

RPW Differences Between Responders and Non-responders

In Cohort 1, computation of RPWs and their dynamics in the recording sites revealed significant changes for both Responders

TABLE 1 | Demographic and treatment data for Cohort 1 and Cohort 2.

		Cohort 1				Cohort 2			
		Combined (*n* = 60)	**Non-responders (*n* = 25)**	**Responders (*n* = 35)**	***p***	**Combined (*n* = 22)**	**Non-responders (*n* = 10)**	**Responders (*n* = 12)**	***p***
Type of epilepsy, *n* (%)	TLE	14 (23)	6 (24)	8 (23)	1.000	6 (27)	3 (30)	3 (25)	0.801
	Extra-TLE	43 (72)	18 (72)	25 (72)		15 (68)	6 (60)	9 (75)	
	IGE	3 (5)	1 (4)	2 (6)		1 (5)	1 (10)	0 (0)	
Gender, *n* (%)	Females	34 (57)	17 (68)	17 (49)	0.188	11 (50)	4 (40)	7 (58)	0.670
	Males	26 (43)	8 (32)	18 (51)		11 (50)	6 (60)	5 (42)	
Age (years) at VNS implantation (median, min-max)		33 (15–65)	30 (15–65)	36 (18–63)	0.134	31 (22–71)	26 (22–42)	40 (22–71)	0.069
Age (years) at epilepsy onset (median, min-max)		9 (1–51)	13 (1–27)	6 (1–51)	0.014	10 (0–59)	8 (0–18)	12 (4–59)	0.123
Duration (years) of epilepsy before vagal nerve stimulator implantation (median, min-max)		22 (4–60)	15 (4–55)	26 (7–60)	0.019	20 (2–49)	20 (14–34)	19 (2–49)	0.872
Duration (years) of VNS (median, min-max)		6 (3–11)	6 (3–10)	6 (3–11)	0.581	3 (2–3)	3 (2–3)	3 (2–3)	0.628
Treatment at the time of VNS implantation, *n* (%)	BRV	2 (3)	2 (8)	0 (0)	0.169				
	CBZ	32 (53)	15 (60)	17 (49)	0.439	9 (41)	3 (30)	6 (50)	0.415
	CLB	1 (2)	1 (4)	0 (0)	0.417				
	CLZ	13 (22)	6 (24)	7 (20)	0.758	4 (18)	3 (30)	1 (8)	0.293
	ESL	3 (5)	2 (8)	1 (3)	0.565	5 (23)	4 (40)	1 (8)	0.135
	GBP	1 (2)	0 (0)	1 (3)	1.000				
	LCM	6 (10)	1 (4)	5 (14)	0.386	9 (41)	6 (60)	3 (25)	0.192
	LEV	36 (60)	16 (64)	20 (57)	0.790	10 (45)	4 (40)	6 (50)	0.691
	LTG	27 (45)	11 (44)	16 (46)	1.000	9 (41)	4 (40)	5 (42)	1.000
	PGB	5 (8)	2 (8)	3 (9)	1.000	1 (5)	0 (0)	1 (8)	1.000
	PHE	1 (2)	0 (0)	1 (3)	1.000				
	PHT	4 (7)	1 (4)	3 (9)	0.634	1 (5)	1 (10)	0 (0)	0.455
	PRM	3 (5)	1 (4)	2 (6)	1.000	2 (9)	1 (10)	1 (8)	1.000
	TPM	13 (22)	5 (20)	8 (23)	1.000	2 (9)	1 (10)	1 (8)	1.000
	VPA	14 (23)	2 (8)	12 (34)	0.028	5 (23)	3 (30)	2 (17)	0.624
	ZNS	8 (13)	5 (20)	3 (9)	0.259	9 (41)	4 (40)	5 (42)	1.000
Number of AEDs used at the time of VNS implantation, *n* (%)	1	4 (7)	1 (4)	3 (9)	0.974	1 (5)	0 (0)	1 (8)	0.495
	2	17 (28)	8 (32)	9 (26)		7 (32)	3 (30)	4 (33)	
	3	26 (43)	11 (44)	15 (43)		7 (32)	2 (20)	5 (42)	
	4	12 (20)	5 (20)	7 (20)		5 (23)	3 (30)	2 (17)	
	5	1 (2)	0 (0)	1 (3)		2 (9)	2 (20)	0 (0)	

AEDs, antiepileptic drugs; BRV, brivaracetam; CBZ, carbamazepine; CLB, clobazam; CLZ, clonazepam; ESL, eslicarbazepine; Extra-TLE, extratemporal lobe epilepsy; GBP, gabapentin; LCM, lacosamide; LEV- levetiracetam; LTG, lamotrigine; NA, not applicable; PGB, pregabalin; PHE, phenobarbital; PHT, phenytoin; PRM, primidone; TLE, temporal lobe epilepsy; TPM, topiramate; VNS, vagal nerve stimulation; VPA, valproic acid; ZNS, zonisamide.

and Non-responders in all investigated frequency bands, all defined conditions, and the majority of electrodes (**Figure 3**). These changes were largely equivalent for both Responders and Non-responders within specific frequency bands and conditions. In the alpha and gamma frequency bands, however, there were striking dissimilarities between the two patient groups in conditions, with the most prominent differences during photic stimulation (PS) and hyperventilation (HV). Comparing Responders and Non-responders with respect to the RPW in all pre-defined frequency bands and conditions, we revealed significant differences in alpha and gamma frequency bands (**Figure 4**).

When analyzing the alpha band, significant differences between Responders and Non-responders were found in the following conditions: 4-PS, 5-HV, and 8–Rest#4. The differences were present over different brain regions in each condition: In 4-PS, there were differences over central and anterior areas (absence of desynchronization in Responders); in the 5-HV interval we observed differences over central and posterior regions (significantly higher synchronization in Responders); and in 8-R, differences were localized to right anterior and left posterior areas (higher power in Responders but persisting desynchronization in Non-responders).

When focusing on the gamma frequency band, we observed significant differences (gamma synchronization in Responders and desynchronization in Non-responders) in RPW within 4-PS, 5-HV and 7-Rest#3: In the first two conditions, differences were distributed across almost the whole scalp. The differences in RPWs within 7-Rest#3 were observed within right anterior and left posterior areas.

Prediction of VNS Response—Statistical Model

Based on the EEG data of Cohort 1, the statistical model was developed. Eight groups of electrodes were selected as the most discriminative in this statistical model (visualized in **Figure 5**). The best classification results based on these eight most discriminative groups of electrodes were obtained using the LR classifier, achieving 86.7% accuracy, with 88.6% sensitivity and 84% specificity (**Table 2**). This classification accuracy was significantly higher than those achieved by chance ($p < 0.001$). The SVM classifier achieved lower accuracy (75%) but it was still significantly higher than that achieved by chance ($p = 0.004$). The lowest classification performance measures were obtained in classification using LDA (accuracy 65%). Detailed visualizations of classification accuracy are provided in **Figure 6**.

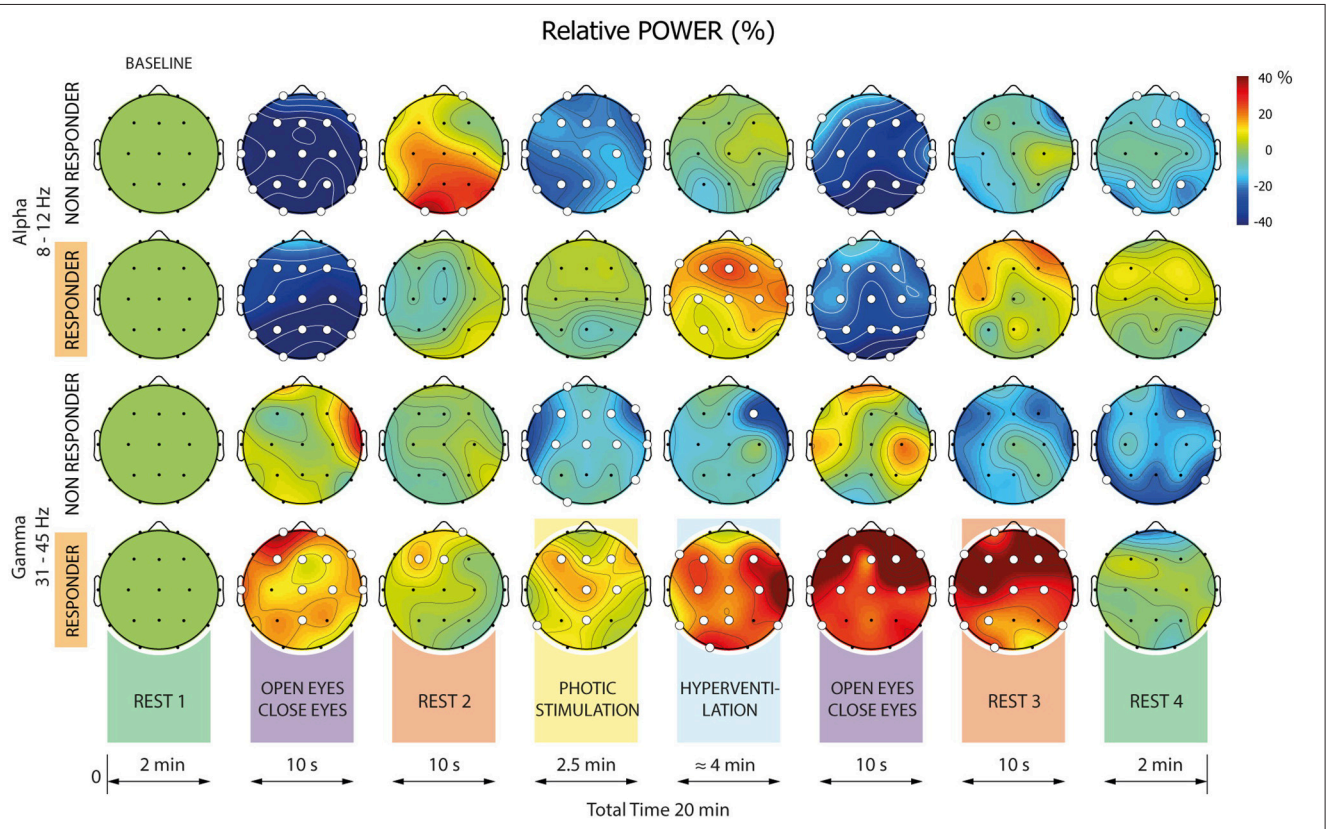

FIGURE 3 | Relative mean powers (RPWs) for all frequency bands. Each head represents RPW in a given condition and frequency band. The RPW percentage scale is displayed on the right-hand side. Where a statistically significant difference exists in a given condition relative to baseline (Rest#1), the electrode is marked by a white dot. If no significant difference exists, the electrode is marked by a black dot.

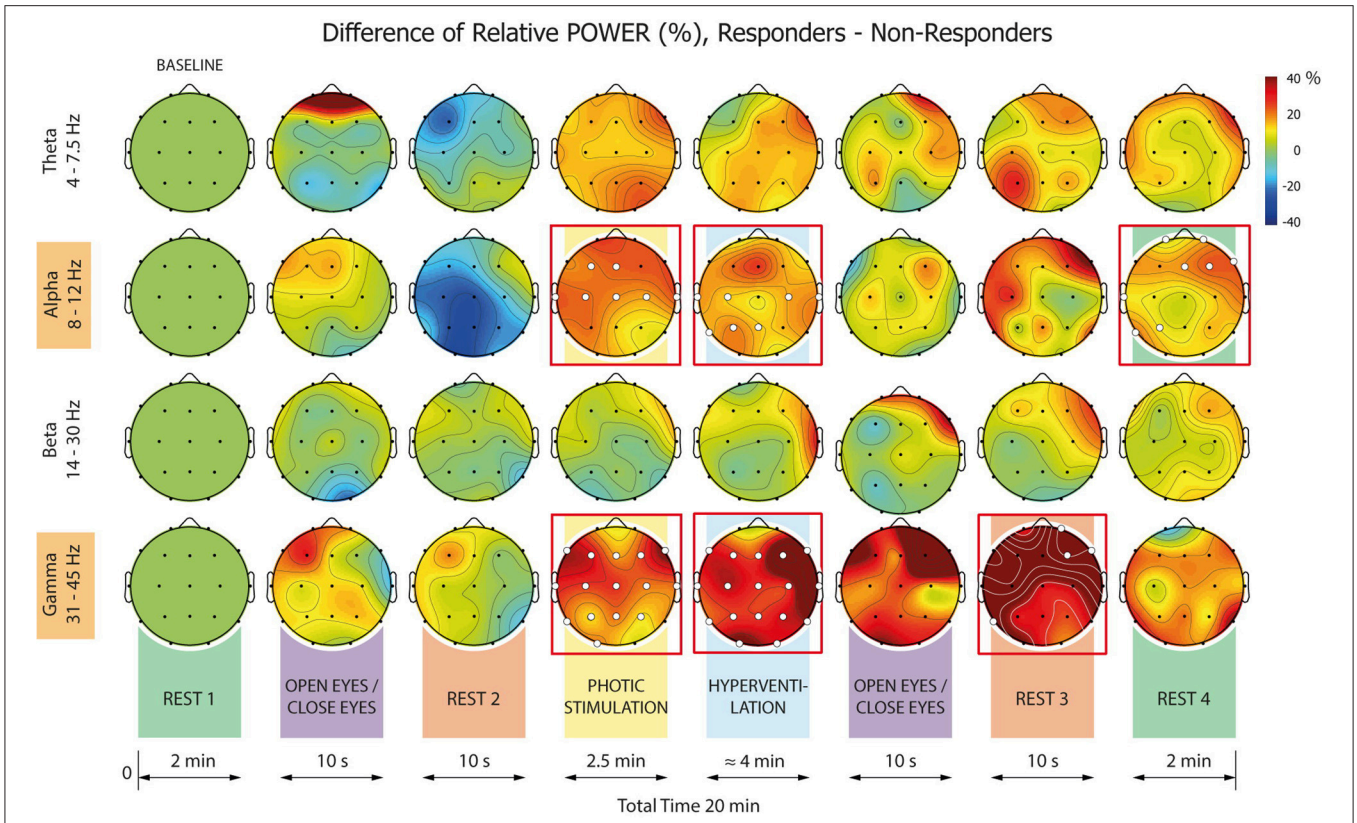

FIGURE 4 | Relative mean power (RPW) differences between Responders and Non-responders. Statistically significant or non-significant differences in a given electrode are marked by a white or black dot, respectively. The significant differences between Responders and Non-responders were identified in alpha and gamma frequency ranges only (heads in red boxes).

The final statistical model is described in more detail in **Supplementary Material 3**.

Validation of the Statistical Model

The data of patients in Cohort 2 were used for independent validation. When comparing the results of our classification model applied to Cohort 2 against real-life outcome, the best results were again obtained for the model using the LR classifier achieving an accuracy of 86.4%, sensitivity of 83.3%, and specificity of 90%. The complete results achieved using classifier voting are summarized in **Table 2**. Classification performance based on a single classifier was lower (data not shown).

DISCUSSION

Over 80,000 epilepsy patients have been treated worldwide using vagal nerve stimulation (VNS), a standard of modern non-pharmacological treatment. Importantly, the number of epileptic patients who are eligible for VNS therapy is approximately three million subjects worldwide. In this light, a method for the reliable prediction of individual efficacy of VNS therapy is desperately needed.

Recently, several authors have attempted to identify predictors of VNS outcome (1, 2, 4, 13). Despite these efforts, however, clinical predictors of individual responsiveness to VNS therapy remain elusive. Similar estimates of efficacy are reported for diverse neurostimulation techniques in the treatment of drug-resistant epilepsy (i.e., VNS, Deep Brain Stimulation of Anterior Thalamic Nuclei, Brain Responsive RNS System, transcutaneous VNS, or external Trigeminal Nerve Stimulation), which might suggest a more consequential impact of external stimuli *per se* on epileptic activity. For this reason, we retrospectively evaluated routine EEG data acquired before implantation in a large cohort of VNS patients. Using standard computations of power spectral analyses of interictal EEG, we reveal significant differences between responders and non-responders in two pre-defined frequency bands (alpha and gamma) and four conditions of standard clinical assessment. Based on RPWs and their dynamics, we have developed and validated a statistical model for prediction of VNS efficacy that discriminated between responders and non-responders with almost 90% accuracy.

Our primary finding is that VNS responders and non-responders differ significantly in EEG power dynamics within alpha and gamma frequency bands prior to therapy. Whilst both patient groups demonstrated equivalent alpha desynchronization during eyes opening, they differed in alpha reactivity to photic stimulation and hyperventilation; specifically, responders showed no decrease in alpha power during the former but

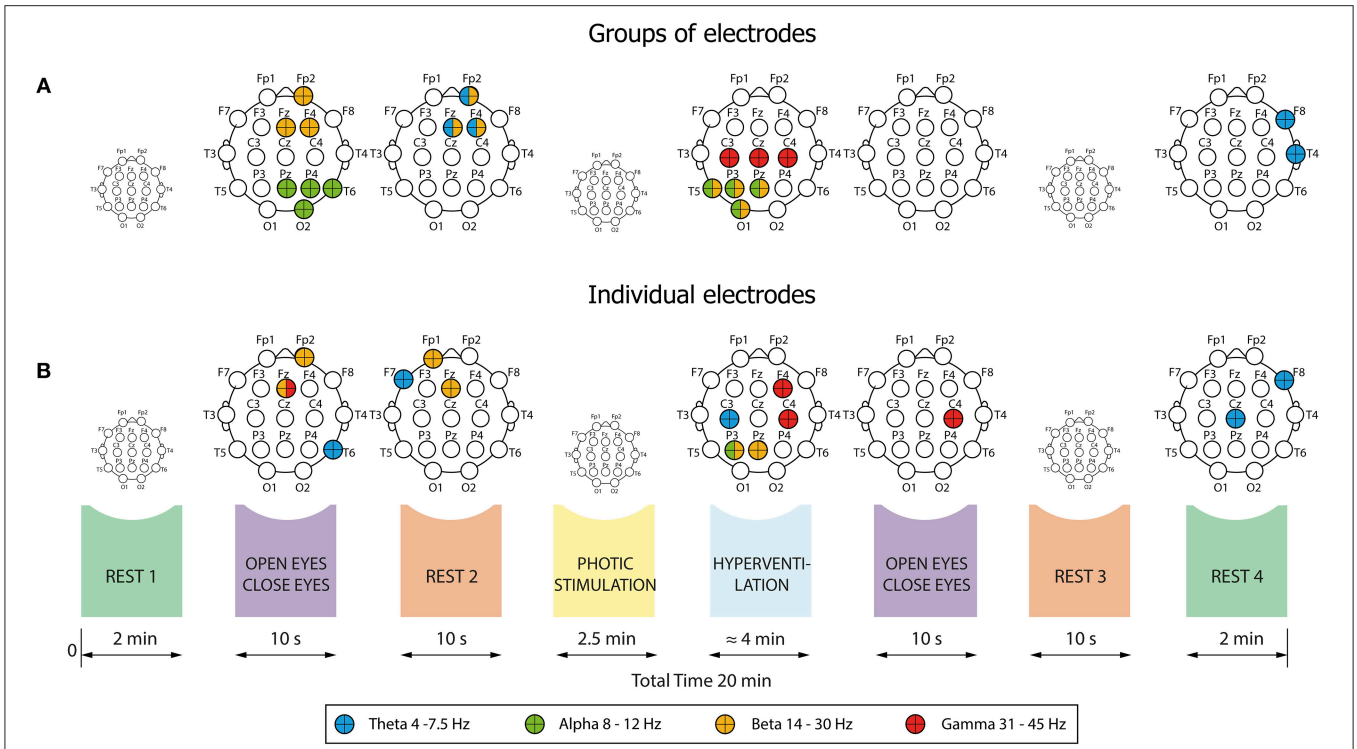

FIGURE 5 | Electrode groups and individual electrodes selected for statistical modeling. Electrode groups **(A)** and individual electrodes **(B)** selected for the development of the statistical model, in each condition and frequency band.

TABLE 2 | Classification performance indices for electrode group variables.

	Cohort 1–60 patients				Cohort 2–22 patients			
	Accuracy	**Sensitivity**	**Specificity**	***p***	**Accuracy**	**Sensitivity**	**Specificity**	***p***
LR	86.7	88.6	84.0	<0.001	86.4	83.3	90.0	0.006
SVM	75.0	62.9	92.0	0.004	77.3	58.3	100.0	0.043
LDA	65.0	48.6	88.0	0.147	45.5	16.7	80.0	0.879

LDA, linear discriminant analysis; LR, logistic regression; p, p-value calculated using one-sample binominal test; SVM, linear support vector machines.

an enormous increase during the latter. This reactivity pattern stands in contrast to that observed in healthy individuals, in whom photic stimulation typically leads to alpha attenuation and standardized hyperventilation has been shown to decrease alpha power (14). Interestingly, we also observed significant increases in gamma power during both photic stimulation and hyperventilation in responders relative to non-responders. Hyperventilation-induced physiological changes are thought to be a consequence of increased neuronal excitability resulting from the hypocapnia-induced alkalosis (15, 16). Significantly enhanced alpha and gamma activities during hyperventilation in responders might reflect distinct properties of responders' brains vis-a-vis neuronal excitability and synaptic transmission. Nevertheless, hyperventilation is a complicated practice which, in epileptic subjects, results in unpredictable responses. The reasons for this remain unclear (e.g., metabolic hypersynchronization, altered neurotransmitters, etc.). It also remains unclear why the alpha (and less expressed gamma) desynchronization persist in our non-responders at the end of EEG recordings (Rest#4). It seems that the protocol itself, particularly photic stimulation and hyperventilation, induces some change from the resting-state baseline for non-responders. Differential dynamics of power changes after the stimulation—faster in responders and slower in non-responders—might represent another characteristic in which these groups of patients differ substantially.

Interestingly, valproic acid (VPA) was used more frequently in pharmacological treatment prior to implantation in our VNS responders compared to the non-responders. We might therefore ask whether differences in EEG reactivity observed in our study is related to some pharmacological imprint. Although this speculative explanation cannot be fully excluded, it seems unlikely that pharmacological impact on EEG is the main factor driving our findings. Still more unlikely is substantial VPA impact on the prediction of VNS efficacy, bearing in mind that only one third of responders were treated with VPA and the accuracy of individual VNS efficacy prediction was almost 90%.

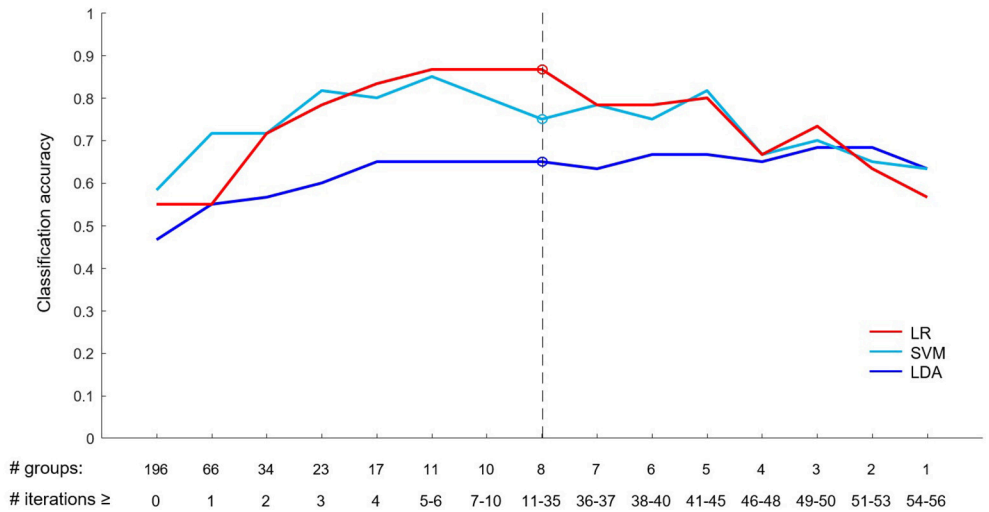

FIGURE 6 | Classification accuracy based on a number of selected groups of electrodes. The bottom row of numbers shows a minimum number of LOO iterations (# iterations) in which a given number of electrode groups (# groups) were selected as most discriminative (e.g., eight electrode groups were selected as maximally discriminative in 35 or more LOO iterations). The best LR classification accuracy and corresponding results for SMV and LDA (shown in **Table 2**) are depicted by circles and a dashed line.

Since Hans Berger's initial observation in 1933, the best known example of EEG reactivity is alpha attenuation (alpha blocking and desynchronization). This is observed typically when subjects open their eyes (the Berger effect), but alpha also disappears when subjects become drowsy and it can be blocked by numerous kinds of external stimuli (visual or auditory) or mental operations (e.g., imagery, visualization, mental arithmetics). This implies that alpha reactivity as a modality-independent, general phenomenon, reflecting the functional modes of thalamo-cortical and cortico-cortical loops that facilitate/inhibit the transmision of information in the brain (17, 18). Particularly noteworthy is the high inter-individual variability in alpha reactivity; it has been shown to differ between extraverts and introverts, for example, and there is less pronounced alpha desynchronization in people with high intelligent quotient during several cognitive tasks (19, 20). Alpha reactivity has also been reported to decrease with aging (21–24) and in patients with mild cognitive impairment and Alzheimer disease (25), and a lack of alpha reactivity has been used to predict the long-term deterioration of higher functions in subjects with cognitive decline (26). From this viewpoint, our discovery of differential alpha reactivity in VNS responders vs. non-responders further emphasizes the multifold functions of the diffuse alpha system (27).

In our study, significant differences in EEG power dynamics within the gamma frequency band between VNS responders and non-responders very likely reflects distinct reactivity of true brain gamma. When interpreting thoroughly our results in this frequency band, however we shall keep in mind the study of Whitham et al. (28); these authors showed recently that even the normal resting EEG might reveal significant contamination with electromyography (EMG) activity in this frequency band. Further, the level of EMG contamination increased dramatically when subjects perform various experimental tasks and are sitting during EEG recordings (29). More recently, however, Boytsova et al. showed that EMG contamination does not necessarily hide high-frequency EEG and does not preclude qualitative detections of electroencephalographic correlates of mental activities in beta and low gamma frequency ranges (30). Unfortunately, despite the availability of several techniques for the reduction of muscular artifacts from EEG traces, at a present none are able to guarantee that analyzed data are completely free of high-frequency artifacts (29). In our study, EEG was recorded under standard conditions: patients laid comfortably and were instructed to relax (including their facial muscles), no task was performed, and recordings from patients containing artifacts identified with careful visual inspection (e.g., muscular activity) were excluded (17 out of 110 patients). As such, we strongly believe an increased gamma power during both photic stimulation and hyperventilation in responders relative to non-responders is not resulting from distinct muscle artifacts contaminations.

Both brain rhythms—alpha and gamma—are considered to represent a kind of universal code consistent with their putative role in brain signaling (27). Both are generated in a widely distributed system, with a major role of thalamocortical circuits in their origin (31–33). The differential impact of external stimuli on alpha and gamma between VNS responders and non-responders might be mediated by differences in neuronal interconnectivity and different levels of neurotransmitters within underlying cerebral matrices (24). Such differences might influence the effect of external stimuli delivered to thalamocortical circuits and other brain networks via the vagal nerve (34, 35). Consistent with this notion, many consider the mechanism of VNS action to be modulation of synaptic activity in the thalamus and thalamocortical projections, increased plasticity in GABA receptors, and modulation of GABAergic activity that is related directly to

gamma oscillations (6, 36). Indeed, one of the most plausible factors involved in gamma variation between our populations of responders vs. non-responders is represented by the role of GABA neurotransmission and divergent dynamics of inhibitory interneuron networks within the central nervous system (37, 38). The close relationship between different types of external stimulation and brain reactivity we have observed might be indicative of a common mechanism underlying the various forms of neurostimulation in epilepsy treatment.

Finally, as seen in the developed and validated statistical model, for accurate prediction of VNS efficacy distinct recording electrode groups, different conditions (especially hyperventilation, but also eyes opening/closing and resting periods), and all frequency bands were selected as the most discriminative ones. Using our approach we achieved high accuracy, sensitivity and specificity in both well-defined and predominant VNS patients. We also evaluated a statistical model based on single electrodes, which had slightly superior classification performance in Cohort 1 and predominant VNS patients but failed in the independent validation set of Cohort 2. This indicates that groups of electrodes are better suited for VNS efficacy prediction—by integrating data from larger regions, such groupings appear to produce more robust results.

To conclude, we have revealed that EEG reactivity to external stimuli used during routine pre-operative EEG investigation differs between VNS responders and non-responders. Moreover, we have developed and validated a statistical tool that can predict with extremely high accuracy whether or not individual drug-resistant epileptic patients will benefit from VNS treatment (Patent Number EP3437692-A1). This electrophysiological marker could prove invaluable when providing patients with expected postoperative prognosis. Further research is required before this can be achieved, however; our findings come from a retrospective and monocenter study, with a limited number of patients comprising the independent validation. Our results must therefore be replicated in prospective, multicentre, and well-designed clinical study in order to obtain a clear-cut statistical power.

ETHICS STATEMENT

Ethic committee in St. Anne's University hospital approved this study. All patients gave their informed consent.

AUTHOR CONTRIBUTIONS

MB, RR, PJ, JChr, and DS: identification of research topic, preparation of study design, interpretation of results. ID and MP: preparation of manuscript, design of study, interpretation of results. JChl and PJ: mathematical analysis. EK: statistical analysis.

FUNDING

The results of this research have been acquired within CEITEC 2020 (LQ1601) project with financial contribution made by the Ministry of Education, Youth and Sports of the Czech Republic (MEYS CR) within special support paid from the National Programme for Sustainability II funds, MEYS CR project LO1212, and the Ministry of Health of the Czech Republic, grant nr. NV19-04-00343.

ACKNOWLEDGMENTS

We would like to thank Matthew C. Walker for his valuable help and advice with manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.00392/full#supplementary-material

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Conflict of Interest Statement: The patent application was applied (patent applicant Masaryk University; inventors are the authors of the manuscript: MB, ID, EK, JChl, RR, JChr, MP).

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Annex 14: Plešinger F, Halámek J, Chládek J, Jurák P, **Doležalová I**, Chrastina J, Brázdil M. Response to vagal stimulation by heart-rate feature in drug-resistant epileptic patients. Annual International Conferences of the IEEE Engineering in Medicine and Biology Society 2020:46-49.

Response to Vagal Stimulation by Heart-rate Features in Drug-resistant Epileptic Patients*

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Abstract— **Vagal Nerve Stimulation (VNS) is an option in the treatment of drug-resistant epilepsy. However, approximately a quarter of VNS subjects does not respond to the therapy. In this retrospective study, we introduce heart-rate features to distinguish VNS responders and non-responders. Standard pre-implantation measurements of 66 patients were segmented in relation to specific stimuli (open/close eyes, photic stimulation, hyperventilation, and rests between). Median interbeat intervals were found for each segment and normalized (NMRR). Five NMRRs were significant; the strongest feature achieved significance with p=0.013 and AUC=0.66. Low mutual correlation and independence on EEG signals mean that presented features could be considered as an addition for models predicting VNS response using EEG.**

Clinical Relevance— **Responders and non-responders to VNS can be distinguished (with low AUC) also by heart activity.**

I. Introduction

Drug-resistant epilepsy can be treated by resective surgery (if localized) or by vagal nerve stimulation (VNS). Although the VNS is less interventing to a patient, it is less effective and usually does not lead to complete seizure freedom. Approximately half of the patients show a decreased amount of seizures by 50%; a quarter of the patients does not respond to the VNS [1], [2] at all.

In general, epilepsy research usually uses electroencephalograph (EEG) signals to measure brain activity. This also applies to works focused on explaining the mechanism of the VNS effect [3]–[5] investigating synchronization/desynchronization of EEG in specific frequency bands. Yet up to this date, features and models predicting response to the VNS are missing [2] with exception to [6]. However, presented studies were focused on information from the brain while information describing heart activity, electrocardiogram (ECG), remains unused except for [7] using HRV analysis from 24-hours ECG recordings.

* This research has been financially supported by grant AZV NV 19-04-00343

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In this retrospective study, we investigated features derived from ECG signals; we explored their ability to distinguish between responders and non-responders to VNS therapy in drug-resistant epileptic patients.

II. Data

Subjects to VNS were measured in the Brno Epilepsy Center (Brno, Czech Republic) between 2005 and 2015 as a standard pre-operative assessment. These measurements were part of a study [6] focused on relations between scalp EEG signals and VNS response. After the VNS implantation, patients were followed-up (≥ 2 years), and individual outcomes were evaluated based on seizure reduction [8]: patients with < 50% reduction were considered as non-responders while others were considered VNS responders.

A. Patients

In this analysis, we used a subgroup of patient cohort presented in the source study [6]. Patients were removed from the presented analysis when measurement protocol was not respected, or unexpected events occurred (coughing during hyperventilation, sleep). Finally, a total of 66 patients (age 34 ± 12 years) consisting of 30 men and 36 women with 36 responders and 30 non-responders formed the cohort for this analysis (Tab. 1).

TABLE I. Patient cohort

Gender	Patient cohort		
	All	***Responders***	***Non-responders***
All	66	36	30
Females	36	18	18
Males	30	18	12

B. Protocol description

A standard protocol (Fig. 1) was used for measurements:

- rest at the beginning with closed eyes (Rest 1)
- open eyes for 9 seconds
- the second rest (Rest 2)
- photic stimulation with increasing and decreasing frequency from 5 to 50 Hz
- the third rest (Rest 3)
- hyperventilation using nose
- hyperventilation using mouth
- the fourth rest (Rest 4)
- second block with open eyes

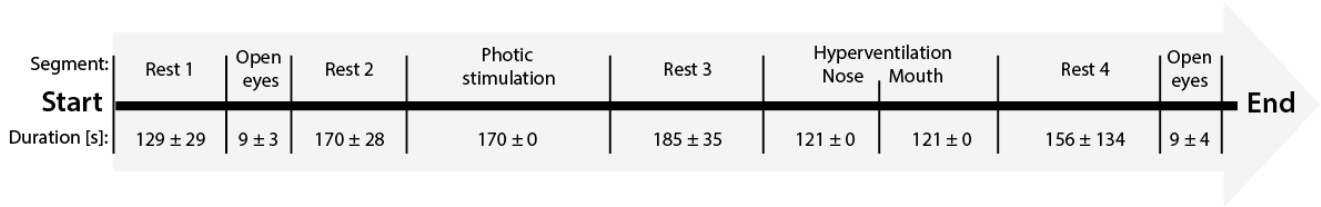

Figure 1. Protocol design with segment names and mean durations

C. Recordings

ECG signals were recorded together with EEG signals using Alien Deymed device with standard 10-20 electrode placement. Recordings were sampled at 128 Hz. If more then one ECG channel was available, the first one was used. Recording device provided antialiasing filtering for all input signals.

III. METHOD

A. Measurement segmentation

Each measurement was split into segments based on individual marks. Because this analysis works with heart activity, a sufficient length of time segments is needed. Therefore, the duration of rest segments is higher in comparison to the rest segments used in the source study [6]. In total, each recording was split into nine segments.

B. The segment-specific median RR interval (MRR)

Heartbeats (QRS complexes) were found for each measurement segment. For this purpose, we used a technique based on amplitude envelopes developed for the ECG Holter study [9]. This technique transforms input ECG signal into amplitude envelope in band 5-25 Hz, searches for local maxima, and applies several rules to deny or accept specific peak as a QRS. Then an array of inter-beat (RR) intervals for each segment is computed as a difference of QRS positions. Finally, the MRR is computed as a median of the array.

C. Baseline normalization

As RR intervals are specific to patients, they need to be normalized to a baseline. It is a crucial part of this study since the significance of heart-rate features strongly relates to used baseline. As a baseline, we used the rest between the end of deep breathing and the last opening of eyes (Rest 4). Therefore, normalized MRR (NMRR) of each segment is computed as

$$NMRR_{seg} = \frac{MRR_{seg}}{MRR_{Rest\ 4}}$$

where *seg* refers to a specific measurement segment. Selection of the segment Rest 4 as a baseline is based on systematical search over all segments (discussed in chapter V, point A).

D. Statistical analysis

Statistical analysis of NMRR values was processed using Python 3.7 and a SciPy [10] package. Non-parametric Wilcoxon–Mann–Whitney test [11] was used to evaluate the ability of each NMRR to separate responders and non-responders. P-values lower than 0.05 were considered significant. Also, the Area under the Receiver-Operator Curve (AUC) was computed for each measurement segment. A linear relationship between significant features was examined using a correlation matrix.

IV. RESULTS

A. Median RR values in segments

MRR values do not show significant differences between VNS responders and non-responders in any of the segments (Tab. 2). For completeness, the last row of tab.2 shows MRR over the whole measurement, which also remains non-significant.

TABLE II. MEDIAN RR VALUES FOR SEGMENTS

Segment	***Mean of Median RR values [s]***		***p-value***
	Responders [N=36]	***Non-responders [N=30]***	
Rest 1	0.84 ± 0.15	0.83 ± 0.17	0.38
Open eyes 1	0.86 ± 0.15	0.85 ± 0.17	0.43
Rest 2	0.84 ± 0.15	0.83 ± 0.16	0.36
Photic stimulation	0.85 ± 0.15	0.84 ± 0.16	0.32
Rest 3	0.85 ± 0.15	0.84 ± 0.16	0.26
Hyperventilation nose	0.82 ± 0.16	0.81 ± 0.16	0.32
Hypervenilation mouth	0.81 ± 0.16	0.80 ± 0.15	0.39
Rest 4	0.84 ± 0.16	0.85 ± 0.16	0.45
Open eyes 2	0.85 ± 0.15	0.84 ± 0.15	0.34
Overall	0.84 ± 0.15	0.83 ± 0.16	0.38

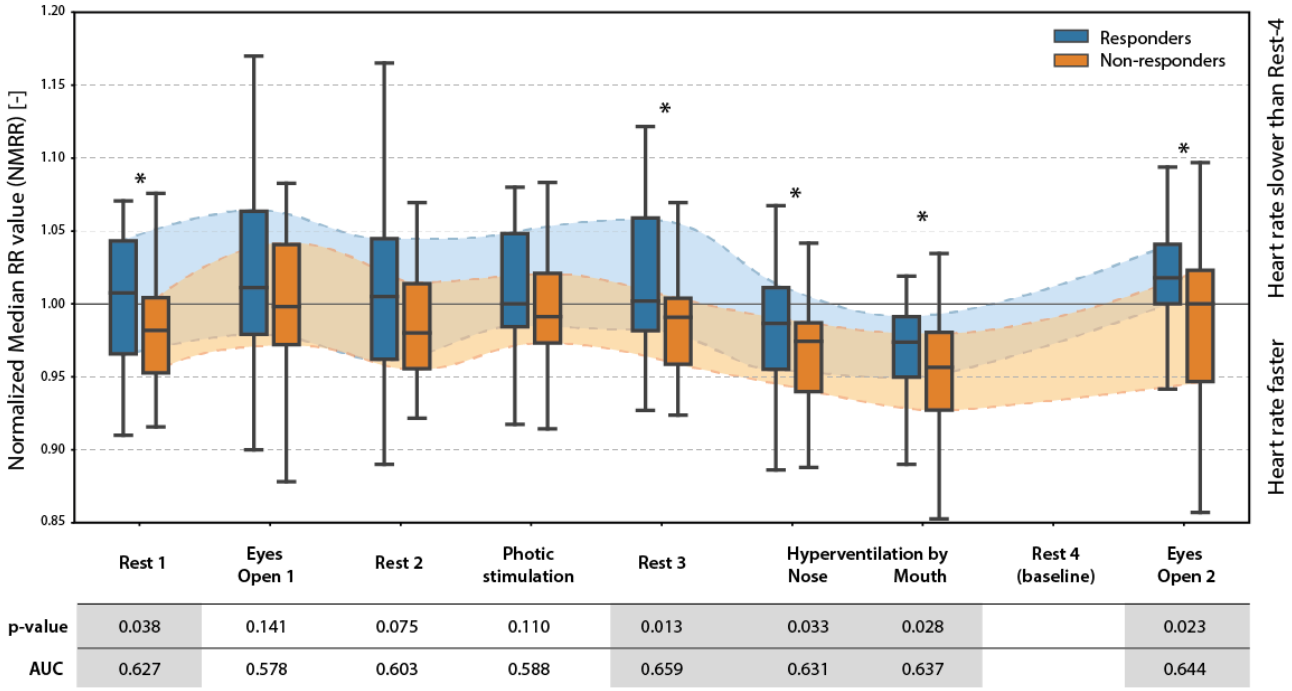

Figure 2. Ability of median RR (MRR) intervals to separate responders (blue) and non-responders (orange). MRR values were normalized to MRR from segment Rest-4. Blue and orange stripes are defined by 1st and 3rd quartile of specific boxplots. Grey areas mark significant features.

B. Normalized Median RR values in segments

On the other hand, different results are obtained when MRR values are normalized to a baseline (Fig. 2 and Tab. 3). We used the Rest 4 as the baseline segment; this normalization revealed five significant features – NMRRs from Rest 1, Rest 3, Hyperventilation by the nose, Hyperventilation by mouth, and the second segment with Open eyes.

TABLE III. NORMALIZED MEDIAN RR VALUES FOR SEGMENTS

Segment	*Mean Normalized Median RR*		*p-value*
	Responders [N=36]	*Non-responders [N=30]*	
Rest 1	1.01 ± 0.07	0.99 ± 0.05	0.038*
Open eyes 1	1.03 ± 0.07	1.00 ± 0.07	0.141
Rest 2	1.01 ± 0.06	0.99 ± 0.04	0.075
Photic stimulation	1.01 ± 0.06	0.99 ± 0.04	0.110
Rest 3	1.01 ± 0.05	0.99 ± 0.03	0.013*
Hyperventilation nose	0.98 ± 0.05	0.96 ± 0.05	0.033*
Hypervenilation mouth	0.97 ± 0.04	0.95 ± 0.05	0.028*
Open eyes 2	1.02 ± 0.06	0.99 ± 0.06	0.023*

Fig. 2 shows differences in NMRR values between responders and non-responders, accompanied by p and AUC values. In those five significant features, we examined mutual correlations (Fig. 3); the strongest correlations were found between two hyperventilation segments (by mouth and nose).

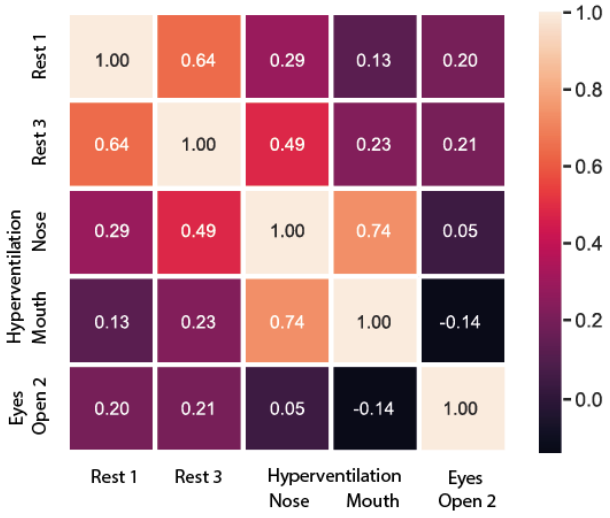

Figure 3. Correlation matrix of significant normalized median RR intervals (NMRR).

V. Discussion

A. Selecting a proper normalization segment

Results showed that features based only on heart activity are weak, but significant for recognizing VNS response. However, this significance depends on the segment used for the normalization. We started with normalization using the median RR interval over the whole measurement as we expected that this could refer to the regular heart rate of the specific patient in the corresponding daytime. However, as shown in the Tab. 4, this normalization led to the only one significant feature – Rest 4. Then we tried normalizing to different measurement segments. Since normalizing to most segments brings none or just one significant feature, we found that normalizing to the Rest 4 brings a surprising amount of significant features.

TABLE IV. SIGNIFICANT FEATURES BY A BASELINE SEGMENT

Baseline segment	**Significant NMRRs**		
	Count	***The most significant NMRR***	
		Name	***p- value***
Rest 1	1	Rest 4	0.038
Open eyes 1	0	-	-
Rest 2	0	-	-
Photic stimulation	0	-	-
Rest 3	1	Rest 4	0.013
Hyperventilation nose	1	Rest 4	0.033
Hyperventilation mouth	1	Rest 4	0.028
Rest 4	**5**	**Rest 3**	**0.013**
Open eyes 2	1	Rest 4	0.023
Overall	1	Rest 4	0.013

B. Possible explanation

Presented observation tells that the long-term response to VNS might be linked with the patient's heart reaction to hyperventilation. More specifically, it might be hypothesized that the epileptic activity enhanced by hyperventilation impacts differentially on brain structures involved in controlling heart rate (e.g., insula or other autonomous brain structures) in responders versus non-responders. An alternative explanation could be that the reactivity of autonomous brain structures to hyperventilation per se is different in responders versus non-responders.

C. Level of significance

All significant features show rather weak AUC values. On the other hand, we are looking at features based purely on the ECG signal, and we are using it for an EEG-specific domain.

D. Features usability

We showed that correlations between significant features in Fig.3 are rather low, which means that several of them could be used together in models predicting VNS response.

E. Method benefits and limitations

The presented method shows significant features based purely on the ECG signal with low mutual correlation. Therefore, presented features could be valuable companions to more common EEG features in models predicting VNS. Introduced ECG features are expectedly weaker then EEG features used in [6]; however, the behaviour of other heart-rate variability features should be investigated. The cohort size of 66 patients is another limitation, and the presented method should be tested on an independent cohort.

VI. Conclusion

In this retrospective study, we have shown that features based only on the ECG signal can significantly distinguish responders and non-responders to vagal nerve stimulation in drug-resistant epileptic patients. We have also shown that the selection of the proper normalization baseline is crucial for feature significance.

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Annex 15: Doležalová I, Kunst J, Kojan M, Chrastina J, Baláž M, Brázdil M. Anterior thalamic deep brain stimulation in epilepsy and persistent psychiatric side effects following discontinuation. Epilepsy Behavior Reports 2019;12:100344.

Epilepsy & Behavior Reports 12 (2019) 100344

Contents lists available at ScienceDirect

Epilepsy & Behavior Reports

journal homepage: www.elsevier.com/locate/ebcr

Case Report

Anterior thalamic deep brain stimulation in epilepsy and persistent psychiatric side effects following discontinuation

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ARTICLE INFO

Article history:
Received 4 August 2019
Received in revised form 27 October 2019
Accepted 28 October 2019
Available online 5 November 2019

Keywords:
Deep brain stimulation of the anterior nucleus of the thalamus
Long-term psychiatric side effects
Case report

ABSTRACT

We report a case of a patient with drug-resistant epilepsy treated with deep brain stimulation of the anterior nucleus of the thalamus (ANT-DBS). The patient developed psychiatric side effects (PSEs), namely irritability, hostility, aggressiveness, and paranoia, after implantation and stimulation initiation. The stimulation was discontinued and the PSEs were mitigated, but the patient did not return to her pre-implantation state, as documented by repeated psychiatric reports and hospitalizations. To our knowledge, this is the first report of a patient who developed long-term PSEs that did not disappear after stimulation discontinuation. We suppose that ANT-DBS caused a persistent perturbation of the thalamic neuronal networks that are responsible for long-term PSEs.

1. Introduction

Deep brain stimulation of the anterior nucleus of the thalamus (ANT-DBS) is a novel and promising treatment method for patients with drug-resistant epilepsy. More than 70% of patients implanted with ANT-DBS benefit significantly from this method, i.e., they report seizure-reduction rates higher than 50% [1]. We have only limited knowledge about short- and long-term ANT-DBS side effects because of relatively low numbers of implanted patients. When focusing on the adverse events reported in a study of stimulation of the anterior nuclei of thalamus (SANTE study), the patients reported paresthesia (18% patients), pain in the implant side (10.9% patients), and infection at the implant site (9.1% patients) [2]. During a five-year follow-up course, device-related adverse events were reported [1]. When focusing on adverse events, depression was present in 37.3% patients (3 events in 3 subjects were considered to be device-related), memory impairment was present in 27.3% patients (approximately a third of memory impairment was confirmed by neuropsychological examination), 11.8% patients reported suicidal ideation (one subject committed suicide; the suicide was not thought to be device related), and 7 patients died during the study — 1 probable sudden unexpected death in epilepsy (SUDEP), 2 definite SUDEP, and 1 possible SUDEP [1].

The anterior nucleus of the thalamus (ANT) has connections with limbic structures, anterior cingulate cortex, and orbitomedial prefrontal cortex; thus, it plays a vital role in memory processes and in emotional and executive functions [3]. A disruption or alteration in baseline circuits can be associated with ANT-DBS psychiatric side effects (PSEs). PSEs can appear immediately after stimulation initialization or can develop over a more extended period. However, in all previously published reports, the PSEs were time-related to stimulation. Järvenpää et al. [9] suggested decreasing the voltage or changing the stimulation contacts to suppress PSEs. At the moment, there is no official recommendation for the management of PSEs in patients with ANT-DBS. We report a patient in whom ANT-DBS caused PSEs that persisted despite stimulation discontinuation. To our knowledge, this is the first report of a patient in whom ANT-DBS caused PSEs not directly linked to the stimulation itself.

2. Case report

The patient is a female born in 1970 with a family history of mesial temporal lobe epilepsy. The patient was treated only for lower back pain and had no history of psychiatric illness. Family history regarding psychiatric disease was also absent. The patient developed epilepsy at the age of 17; the epilepsy was characterized as focal with independent left and right temporal interictal epileptiform discharges and bitemporal seizure onsets during scalp EEG monitoring. Magnetic

Abbreviations: ANT, anterior nucleus of the thalamus; ANT-DBS, deep brain stimulation of the anterior nucleus of the thalamus; MRI, magnetic resonance imaging; PET, positron emission tomography; PSEs, psychiatric side effects.

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https://doi.org/10.1016/j.ebr.2019.100344

resonance imaging (MRI) revealed right-sided hippocampal sclerosis. Positron emission tomography (PET) showed bitemporal hypometabolism. The Wada test demonstrated a crucial role of right-sided mesial temporal structures for verbal memory. The patient was judged to be a poor surgical candidate and neuromodulation was favored. Therefore, the implantation of a vagus nerve stimulator (VNS) was performed at the age of 29. The vagus nerve stimulator was ineffective, which led to its explantation after seven years. The patient was offered ANT-DBS implantation at the age of 41 years. The patient experienced 8 focal seizures with impairment of awareness per month. Before implantation, the psychological examination revealed no severe mental pathology, such as anxiety, depression, or psychosis. However, there were some psychological problems, specifically echolalia, perseveration, and difficulties with management of stressful situations, as well as global deterioration of cognitive function (IQ 72, the most severe alteration in execution and memory). The patient was on stable doses of antiseizure drugs for two years before implantation. She was treated with pregabalin 600 mg/day, zonisamide 400 mg/day, and lacosamide 400 mg/day. The monopolar stimulation of proximal contacts (contact 3 on the left and contact 11 on the right) was initiated one month after ANT-DBS implantation (Fig. 1a and b); the stimulation parameters were as follows: amplitude 2.5 V, stimulation frequency 140 Hz, pulse width 90 ms, 5-minute off-time, 1-minute on-time.

The patient did not note a decrease in seizure frequency, but she did report reduction in seizure severity and duration. Behavioral changes started to appear gradually three months after implantation. The family complained about patient irritability, hostility, and aggressiveness, which were accompanied by newly evolved paranoia. The patient reported that DBS influenced her manners and forced her to walk backward, which worsened when someone was speaking about DBS. A psychological and psychiatric examination performed five months after stimulation initialization revealed incoherent thoughts and behavioral (unrest, agitation) and emotional alteration. Personality and behaviorial disorders were diagnosed. Any possibility of a new structural abnormality was excluded by post-operative magnetic resonance imaging (MRI). We discontinued stimulation and introduced quetiapine (50 mg/day) and subsequently risperidone (1.5 mg/day). This resulted in partial alleviation of the PSEs, but the patient did not reach her pre-implantation state over the next seven years documented by repeated psychological and psychiatric examinations. The patient's state required recurrent psychiatric hospitalizations conditioned by intermittent worsening with psychosis. The patient subjectively reported persistent reduction in seizure severity.

3. Discussion

The anterior nucleus of the thalamus plays a crucial role in seizure generation, as shown in animal and human studies. Stimulation of the anterior nucleus of the thalamus leads to substantial seizure reduction in the majority of patients. The results of two studies suggest that the positioning of the DBS electrode has a significant impact on seizure reduction [4,5]. Patients with electrodes located more anterior and superior [5] or in the antero-ventral part of the thalamus tend to have better responses [4].

The thalamus is a key structure in two core neurocognitive networks, the salience network and the default-mode network, that were proven to play important roles in cognition, emotion, and execution, and that are altered in many psychiatric conditions, including depression, bipolar disorder, schizophrenia, substance use disorder, obsessive–compulsive disorder, and anxiety disorder [6,7]. It is therefore not surprising that interference with the functioning of this structure could be associated with PSEs. ANT-DBS was found to be independently associated with de novo psychopathology in a group of surgically treated patients [8]. Järvenpää et al. [9] reported a group of 22 patients treated with ANT-DBS; four patients developed reversible PSEs. The stimulation induced depression in two patients. The other two patients had symptoms of paranoia and anxiety. In all their patients, the PSEs completely disappeared when they lowered the output current or changed the stimulated contacts [9]. Based on their experience, the authors supposed the stimulation of other thalamic nuclei or tracts close to the ANT to be responsible for PSEs, as the stimulated contacts were not in the ANT itself but beneath.

These findings contrast with our experience. As shown in Fig. 1, the appropriate contact on the left was chosen, the more distal contact was more suitable on the right. Moreover, the PSEs did not disappear after stimulation discontinuation. They persisted for seven years despite intensive treatment with repeated hospitalization. The explanation for this situation is complicated; we can merely speculate about possible reasons. Our hypothesis is that the insertion of electrodes and subsequent stimulation can cause alteration in thalamic circuitry with potential long-term consequences in predisposed individuals such as our patient. We suspect some lesional effect because the PSEs persisted despite stimulation discontinuation similar to thalamic lesions caused by ischemia. Most authors localized the ANT with surrounding nuclei to the territory of the tuberothalamic artery, the closure of which is characterized by severe wide-ranging neuropsychological deficits [10]. Strokes in this arterial territory are associated with the fluctuation of consciousness in the early stage of ischemia. Subsequently,

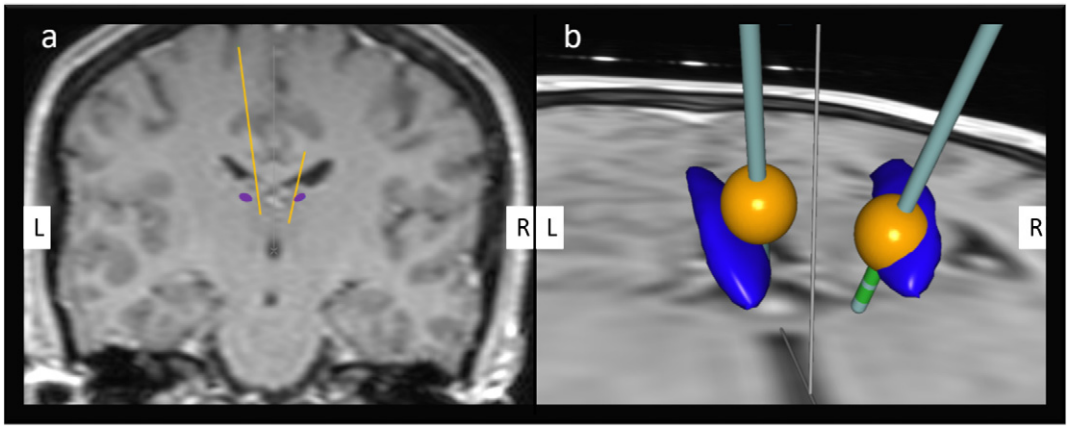

Fig. 1. The position of deep brain stimulation (DBS) electrodes to anterior nucleus thalami (ANT). Panel a illustrates the relation between DBS electrodes and ANT in the coronal section. There are 4 contacts on each electrode (contacts are labeled from the most distal to the most proximal as 0, 1, 2, and 3 on the left, and as 8, 9, 10, and 11 on the right). We stimulated the most proximal contacts on both sides, i.e., contact 3 on the left and contact 11 on the right. Panel b shows the estimated distribution of the electrical field (yellow) and its relation to ANT (blue). On the right, the correct contact for stimulation was chosen. On the left, the more distal contact was more suitable. The figures were obtained using SureTune software (Medtronic, Minneapolis, MN, USA). L — left, R — right.

disorientation, euphoria, lack of insight, apathy, lack of spontaneity, and emotional unconcern can develop [11]. We excluded an acute surgical complication and doubt an adverse effect due to antiseizure drugs was suddenly responsible for the psychiatric complaints in our patient.

ANT-DBS is a promising novel technique for drug-resistant epilepsy treatment, but may be occasionally associated with significant PSEs. It is necessary to inform patients about the possibility of PSEs when offering ANTI-DBS. Because only limited information is available about chronic ANT-DBS PSEs more experience in larger groups of patients is necessary to identify those who are at risk for long-term consequences.

Funding

The results of this research have been acquired with the support of the Ministry of Health of the Czech Republic, grant no. NV19-04-00343.

Ethical statement

We confirm that we have read the Journal's position on issues involved in ethical publications and affirm that this report is consistent with those guidelines.

Declaration of competing interest

Neither of the authors has any conflict of interest to disclose.

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Annex 16: Rektor I, **Dolezalova I**, Chrastina J, Jurak P, Halamek J, Balaz M, Brazdil M. High-frequency oscillations in the human anterior nucleus of the thalamus. Brain Stimulation. 2016;9(4):629-631.

Brain Stimulation 9 (2016) 629–631

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Letter to the Editor

High-Frequency Oscillations in the Human Anterior Nucleus of the Thalamus

Dear Editor:

Deep brain stimulation of the anterior nucleus of the thalamus (ANT-DBS) has recently been introduced in therapy for refractory epilepsy and is approved for clinical use in Europe [1]. ANT is a part of the Papez circuitry and is a key structure in the intrathalamic pathways; it also projects to the cingulate gyrus and further to the limbic structures and wide regions of the neocortex, and via the mammillary circuit to the brain stem [2]. ANT stimulation produces EEG changes in the frontal and temporal areas and inhibits seizures [3]. The role played by the ANT in human epileptic seizures and the mechanisms leading to the anti-seizure effects of ANT-DBS have not yet been fully elucidated. Knowledge of processes occurring in the ANT in human epilepsy might improve the understanding of its role. Here we report the first description of inter-ictal and ictal EEG recording in the human ANT.

DBS electrodes were implanted in the ANT of six pharmacoresistent patients with temporal and extratemporal epilepsies who had not responded to vagus nerve stimulation. (Patient characteristics and outcome see Supplementary material I; Table S1). The recordings were approved by the ethics committee; the patients gave their informed consent. A two-step procedure that is usual in Parkinson's disease was used for DBS in epilepsy, i.e. the DBS electrodes were left externalized for several days before the internalization and the implantation of the battery. Video-EEG monitoring was performed during the 3-day period between the two steps of the operation. Depth EEG via the DBS electrodes was performed using the clinical 128-channel EEG system TruScan (Deymed Diagnostic, Alien Technic, Czech Republic) with a sampling rate of 128 and 256 Hz and standard anti-aliasing filters. To record high frequency oscillations (HFO), in four of six patients a 192-channel research machine (M&I; Brainscope, Czech Republic) was used for ≥10 minutes for awake resting EEG recordings with a sampling rate of 5000 Hz. HFO were detected and scored manually in SignalPlant and ScopeWin visualization softwares. Recordings were filtered and checked in the bandpass of 80–2000 Hz. (More about Methods see in the Supplementary material II).

Inter-ictal recordings: No inter-ictal epileptiform discharges were recorded from the DBS electrodes. The rarity of the epileptic discharges is not specific to the ANT; the absence of epileptiform activity had also been observed in the basal ganglia [4]. The recording with a high-sampling EEG revealed HFO of up to 240 Hz, in one case up to 500 Hz, in all four patients (Fig. 1 and Supporting Material I, Table S2). The occurrence of HFOs in the ANT was bilateral. However, a detailed analysis of individual oscillations in monopolar and bipolar montages displayed different phases of HFOs in the left and right ANT (Supplementary material III, Figs. S2 and S3).

Ictal recordings: We recorded eight clinical seizures in four patients with DBS electrodes implanted in the ANT. An early ictal broad-band increase of power occurred in all seizures. A specific ictal epileptiform activity was recorded in one seizure preceding the onset of the clinical seizure by 4 seconds (Supplementary material III, Fig. S4). The first broad-band power increase preceded the onset of the clinical seizure symptoms in three patients by between 32 seconds and four seconds (Fig. 1).

This is, to our knowledge, the first report of HFO occurrence in a human subcortical structure.

Inter-ictal HFO, ripples, in one case fast ripples, were displayed in all patients in whom a high sample rate EEG could be recorded. It has been shown in animal models that the ripples are generated in the cortex and propagate to the thalamus where they excite the inhibitory reticular neurons inhibiting thalamocortical projections [5]. The electrophysiological state of ANT is altered in patients with epilepsy; atypical firing properties of ANT cells were observed in intraoperative microelectrode recordings [6].

A close connection between epilepsy and HFO in the 80–600 Hz range has been repeatedly described [7,8]. As epilepsy is the only reason to implant an electrode in the ANT and no control recordings are possible we cannot be sure about the nature of HFOs. The characteristics of the HFOs recorded in the ANT indicate that this phenomenon may be pathological. The frequency of spontaneous ANT HFO (up to 240 and 500 Hz) was higher than the frequency of physiological ripples in the human hippocampus (80–160 Hz); it overlapped with the frequency of clearly pathological HFO. Fast ripples (200–600 Hz) could be observed in normal neocortex, but not in normal hippocampus and parahippocampal structures [8,9]. The ANT has tight anatomical and functional connection with the hippocampus.

One limit of our work is inherent to the DBS procedure. Notably, patients have no intracranial exploration of cortical epileptogenic areas, and consequently some links, such as the synchronization between the cortex and the ANT, could not be studied. The surface recordings were limited by the necessity of avoiding the area surrounding the implantation sites and by the location of the electrodes under a bandage; thus, the use of scalp EEG data was very limited.

The seizures might have originated at unrecorded cortical sites and propagated to the ANT, but the recorded interictal and ictal phenomena, including the HFO and the epileptiform EEG activity, were generated in this nucleus. The depth electrodes are submerged in the brain tissue and record from their immediate vicinity. The local fields were displayed as EEG, and its modifications occurred both in reference and in bipolar montage, excluding with high probability the volume conduction from other structures, namely from the cortex, or transsynaptic propagation along the cortical–subcortical pathways [10]. Based on our recordings of HFO, of early ictal ANT electrophysiological modifications, and of ictal epileptiform pattern,

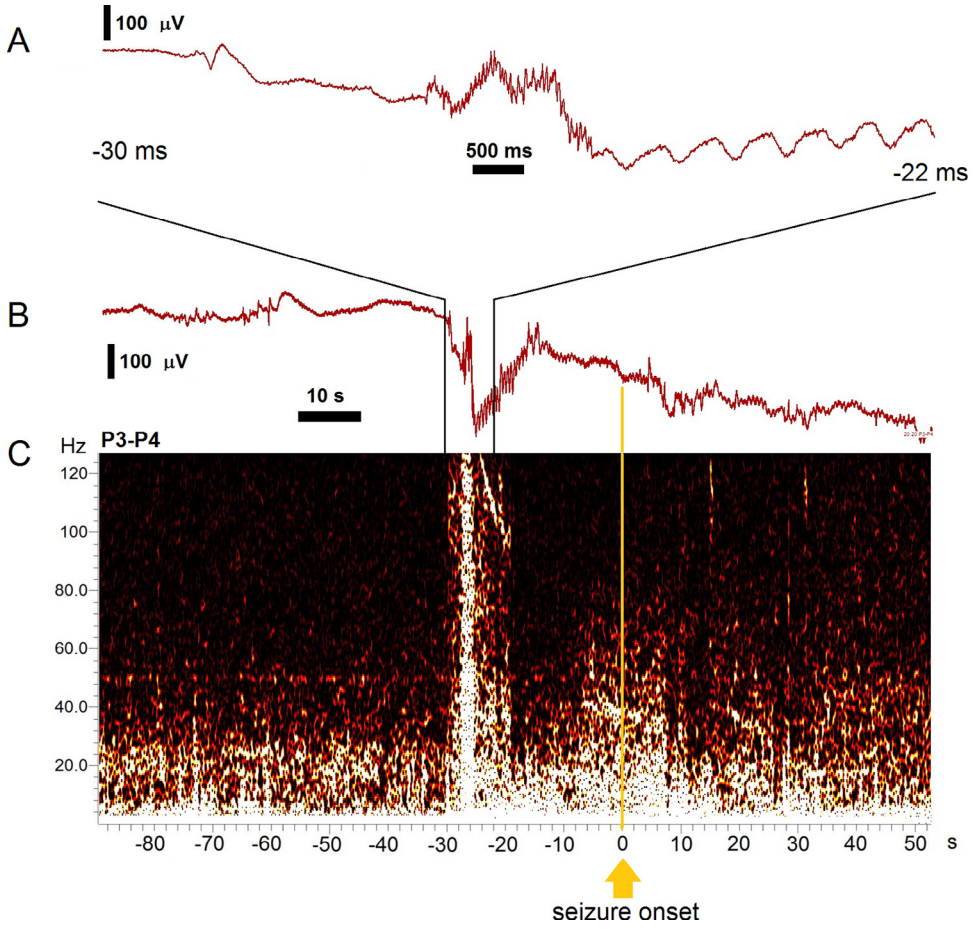

Figure 1. Patient 1. Preictal and ictal recording with high-sampling EEG, bipolar montage, contacts P3-4, right ANT. Time window 90 seconds before and 50 second after the onset of clinical seizure – marked by vertical yellow line at 0s.
A: Enlargement of the signal by zooming at 30–20 s before clinical seizure onset.
B: Raw EEG signal, time window 90 seconds before to 50 second after the onset of clinical seizure marked by vertical yellow line at 0s.
C: Normalized Time Frequency Map (TFM). All values in each TFM frequency row (horizontal line) were normalized to the mean value. Notice enhanced broad-band oscillations with HFO, 30–20 s before the onset of clinical seizure.

we suggest that the ANT may participate directly in the network elaborating clinical seizures in human epilepsies.

Acknowledgments

The authors wish to express their thanks to Dr. Robert Fisher, Stanford, USA, and Dr. Premysl Jiruska, Prague, Czech Republic, for their valuable advices. Supported by the Ministry of Education, Youth and Sports of the Czech Republic under the project CEITEC 2020 (LQ1601).

Appendix. Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.brs.2016.04.010.

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Received 4 April 2016
Available online 14 April 2016

http://dx.doi.org/10.1016/j.brs.2016.04.010

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Epileptochirurgická léčba zlepšuje kvalitu života – výsledky dotazníkové studie

Epilepsy Surgery Improves Quality of Life – Results of a Questionnaire Study

Souhrn

Cíl: Tradičním cílem epileptochirurgické léčby je dosažení bezzáchvatovosti. V současnosti se naše pozornost stále více soustřeďuje na dopad epileptochirurgické léčby na ostatní aspekty života pacienta, nejvíce je řešen její vztah k zaměstnanosti a ke kvalitě života. *Metody:* Pro účely této studie byl na našem pracovišti vytvořen dotazník, který obsahoval 13 uzavřených otázek, jejichž obsah je možné rozdělit do čtyř částí. První okruh otázek zjišťoval obecné informace o nemocném. V druhé části jsme se dotazovali na informace týkající se vlastní operace. Třetí část se zaměřovala na oblast sociální problematiky, konkrétně otázku zaměstnanosti před operací a po ní a držení řidičského oprávnění po operaci. Čtvrtý okruh otázek se týkal subjektivního hodnocení přínosu operace pro pacienta. Odpovědi pacientů byly následně statisticky vyhodnoceny. *Výsledky:* Do studie bylo zařazeno 91 respondentů – 56 mužů (61,5 %) a 35 žen (38,5 %), kteří kompletně vyplnili zaslaný dotazník. U 59 pacientů (64,8 %) po operaci epileptické záchvaty úplně vymizely. Před operací bylo zaměstnáno celkem 46 pacientů (50,5 %), po operaci došlo k mírnému vzestupu zaměstnanosti u čtyř pacientů (4,4 %), tento rozdíl nedosáhl statistické významnosti (p = 0,596). Polovina, konkrétně 49 pacientů (53,8 %), udává pooperačně vzestup kvality života. Poslední otázka zjišťovala, zda by pacient znovu podstoupil operační zákrok, přičemž na tuto otázku většina – 78 pacientů (85,7 %) – odpověděla kladně. *Závěr:* Na základě našeho dotazníkového šetření můžeme říci, že ač velká část pacientů podstoupila úspěšný epileptochirurgický výkon, který je zcela zbavil záchvatů, zaměstnání se podařilo najít jen malé části z nich. I přes tento fakt je epileptochirurgická léčba ze strany našich operantů hodnocena kladně, přináší jim často zvýšení kvality života a většina z nich by znovu podstoupila operační zákrok

Abstract

Aim: Seizure-freedom is the traditional goal of epilepsy surgery. At presents, our attention is more and more concerned with the effects of epilepsy surgery on other aspects, mainly the impact of epilepsy surgery on employment status and quality of life. *Methods:* A questionnaire was designed for the purposes of our study; this questionnaire consists of 13 questions focusing on topics related to epilepsy surgery. These questions could be divided into four subfields: 1. demographic data and patients´ characteristics, 2. information related to surgery, 3. employment and social support, 4. subjective evaluation of surgery impact on the patient's life. *Results:* Ninety-one respondents were included in the study – 56 men (61.5%) and 35 women (38.5%), who correctly completed the questionnaires. Fifty-nine patients (64.8%) were completely seizure-free after surgery. Before the surgery, 46 patients (50.5%) were employed, there was a mild increase in employment after surgery that did not reach statistical significance (p = 0.596). Half of the patients (49, 54%) reported an increase in quality of life after surgery. One question asked whether the patient would undergo the surgery again if he/she could change the past; 78 patients (85.7%) agreed they would. *Conclusion:* The majority of patients undergoing a surgery for drug-resistant epilepsy were seizure-free but only a minority managed subsequently to find an employment. Despite this, epilepsy surgery is assessed positively in the vast majority of patients, it provides them with an increase in quality of life and the majority would undergo the surgery again.

Autoři deklarují, že v souvislosti s předmětem studie nemají žádné komerční zájmy.
The authors declare they have no potential conflicts of interest concerning drugs, products, or services used in the study.
Redakční rada potvrzuje, že rukopis práce splnil ICMJE kritéria pro publikace zasílané do biomedicínských časopisů.
The Editorial Board declares that the manuscript met the ICMJE "uniform requirements" for biomedical papers.

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Přijato k recenzi: 29. 10. 2015
Přijato do tisku: 15. 2. 2016

Klíčová slova

epilepsie – farmakorezistence – chirurgická léčba – bezzáchvatovost – kvalita života – zaměstnanost pacientů po operaci – invalidní důchod

Key words

epilepsy – drug-resistant – surgery – seizure-freedom – quality of life – employment after surgery – disability pension

Úvod

Epilepsie je onemocnění, které postihuje kolem 1 % populace v rozvinutých zemích, je tedy významným problémem jak medicínským, tak i společenským. Pacienti, kteří mají záchvaty i přes správnou léčbu, jsou definováni jako pacienti farmakorezistentní. Farmakorezistentní epilepsie s sebou přináší významná omezení v běžném životě, konkrétně se jedná o zvýšené riziko fyzického poranění či předčasného úmrtí v průběhu záchvatu, sociální problémy a snížení kvality života [1,2]. Přesné vymezení farmakorezistence bylo provedeno v roce 2010 Mezinárodní ligou proti epilepsii (International League against Epilepsy; ILAE). Farmakorezistence je v současnosti definována jako selhání dvou antiepileptik, ať už v monoterapii či v kombinaci [3,4]. U pacientů, kteří plní výše uvedené kritérium, by měly být posouzeny možnosti operační léčby [5]. „Klasickým" měřítkem úspěšnosti epileptochirurgické léčby je vymizení epileptických záchvatů, stále více epileptochirurgických center se však v posledních letech soustřeďuje na dopad operace i na ostatní aspekty oblasti života nemocného [6]. Otázkou zůstává, zda společně s efektem operace dochází u pacienta i ke zlepšení kvality jeho života či možností jeho pracovního uplatnění a k vyšší spokojenosti v osobním a společenském životě [7].

Prezentovaná studie se věnuje výsledkům chirurgické léčby u pacientů s farmakorezistentní epilepsií, kteří podstoupili operační zákrok v Centru pro epilepsie Brno. Vyjma standardního hodnocení vymizení či přetrvávání záchvatů se soustřeďujeme na problematiku sociální (zaměstnanost, invalidita) a problematiku kvality života.

Příloha 1. Dotazník – Kvalita života po epileptochirurgické léčbě.

Otázka č. 1. Jaké je Vaše pohlaví?
- muž
- žena

Otázka č. 2. Kolik Vám bylo v době operace let?
- 18–25 let
- 26–35 let
- 36–45 let
- 46–60 let
- více než 61 let

Otázka č. 3. Jaké je Vaše nejvyšší dosažené vzdělání?
- základní
- učební obor bez maturity
- středoškolské s maturitou
- vyšší odborné
- vysokoškolské

Otázka č. 4. V kterém životním období (věku) jste měl/měla první epileptický záchvat?
- v útlém dětství (do 1 roku věku)
- v dětství (1–10 let)
- v dospívání (11–18 let)
- v dospělosti (18–60 let)
- později než v 60 letech

Otázka č. 5. Jaká doba uplynula od Vaší operace?
- více než 1 rok
- více než 2 roky
- více než 5 let
- více než 10 let

Otázka č. 6. Vymizely u Vás záchvaty po operaci?
- ano
- je jich méně
- ne
- ano, ale mám po operaci jiné obtíže, u kterých si myslím, že souvisí s epilepsií/s vlastní operací (specifikujte jaké)

.....

Otázka č. 7. Byl/byla jste před operací zaměstnán/zaměstnána?
- ano – zaměstnanec nebo osoba samostatně výdělečně činná (OSVČ)
- ne

Otázka č. 8. Pobírala jste před operací invalidní důchod?
- ano
- ne

Otázka č. 9. Jste nyní po operaci zaměstnán/zaměstnána?
- ano – zaměstnanec nebo OSVČ
- ne

Otázka č. 10. Pobíráte nyní po operaci invalidní důchod?
- ano
- ne

Otázka č. 11. Získal/získala jste po operaci řidičské oprávnění (řidičský průkaz)?
- ano
- ne

Otázka č. 12. Jak byste hodnotil svoji kvalitu života po operaci ve srovnání s kvalitou života před operací? Moje kvalita života se:
- zvýšila
- snížila
- je stále stejná
- nevím

Otázka č. 13. Představte si, že byste mohl/mohla vrátit čas. Nechal/nechala byste se znovu operovat?
- ano
- ne
- nevím

Metodika

Pro účely této studie byl na našem pracovišti vytvořen dotazník (příloha 1), který obsahoval 13 uzavřených otázek. Dotazník byl vytvořen tak, aby otázky byly jednoduché a srozumitelné a pacient je byl schopen vyplnit samostatně bez pomoci lékaře či psychologa. Obsah dotazníku je možné rozdělit do čtyř okruhů. První okruh zjišťoval obecné informace o nemocném (pohlaví, věk v době operace, nejvyšší dosažené vzdělání a věk, ve kterém se u pacienta epilepsie objevila). V druhém okruhu jsme se dotazovali na informace týkající se vlastní operace (kolik let uplynulo od operace, zda je pacient bez záchvatů). Třetí část se zaměřovala na oblast sociální problematiky (otázka zaměstnanosti před operací a po ní, pobírání invalidního důchodu před operací a po ní, držení řidičského oprávnění). Čtvrtý okruh otázek se týkal subjektivního hodnocení přínosu operace pro pacienta. V rámci tohoto okruhu byly položeny dvě otázky. První se týkala kvality života po operaci. Druhá otázka byla hypotetická a zněla, zda by se pacient nechal znovu operovat, kdyby mohl vrátit čas.

Dotazník byl rozeslán celkem 137 pacientům, kteří byli operováni v rámci Centra pro epilepsie Brno, podmínkou bylo, že od operace uběhla doba nejméně jednoho roku. Dodržení tohoto časového intervalu jsme považovali za důležité pro validní hodnocení výsledků šetření. Sběr dat probíhal v období prosinec 2012–březen 2013.

Statistika

Všechny proměnné byly nejdříve popisně sumarizovány a srovnány Fisherovým exaktním testem nebo McNemarovým testem. Pro modelování byl použit logistický regresní model. Nejprve byly vyhodnoceny jednorozměrné modely. Dále byly vytvořeny maximální modely, a to zpětnou, dopřednou

i kombinovanou selekcí příznaků. Výstupem modelů jsou tabulky, ve kterých jsou uvedeny poměry šancí (OR) s intervalem spolehlivosti (IS) a p hodnotou. V tabulkách je u kategoriálních proměnných uvedena nejprve riziková a poté referenční kategorie. U výsledného vícenásobného modelu je uvedena hodnota pseudo R2, tzv. Nagelkerke R2, který je počítán jako podíl věrohodností nulového a plného modelu. Jeho největší možnou hodnotou je 1, pokud model perfektně predikuje výsledek s věrohodností 1. Analýza byla provedena v softwaru IBM SPSS Statistics 22 a software R3.1.3. Všechna srovnání byla provedena na hladině významnosti α = 0,05.

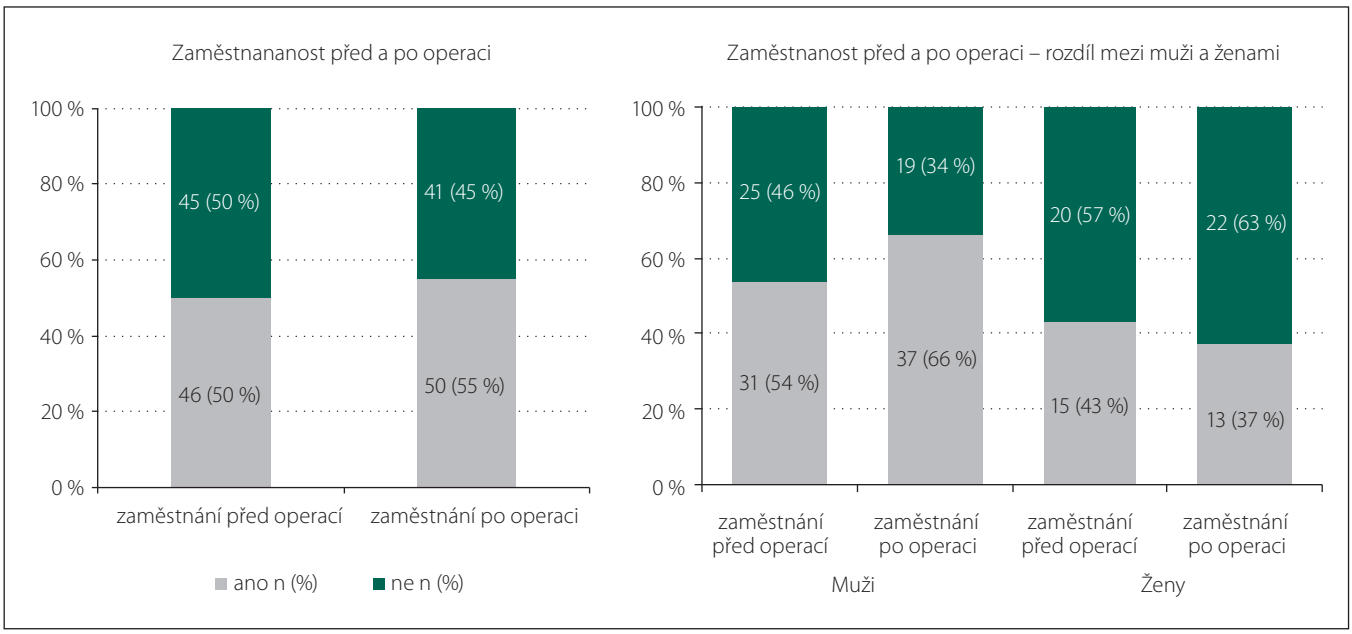
Výsledky

Demografická data

Do studie bylo zařazeno 91 respondentů, 56 mužů (61,5 %) a 35 žen (38,5 %), kteří kompletně vyplnili zaslaný dotazník. Většina, konkrétně 62 pacientů (68,1 %), byla z věkové kategorie 36–60 let, 28 pacientů (30,8 %) bylo z věkové kategorie 18–35 let, jen jeden pacient byl starší 60 let (1,1 %). Pouze u devíti pacientů (9,9 %) se objevily epileptické záchvaty do jednoho roku věku, u 32 v dětství (35,2 %), u 25 v dospívání (27,5 %) a u 25 v dospělosti (27,5 %). Čtyřicet pět pacientů (49,5 %) absolvovalo učební obor bez maturity, 23 pacientů (25,3 %) mělo středoškolské vzdělání s maturitou, 11 pacientů (12,1 %)

Tab. 1. Demografická data pacientů a výsledky chirurgické léčby.

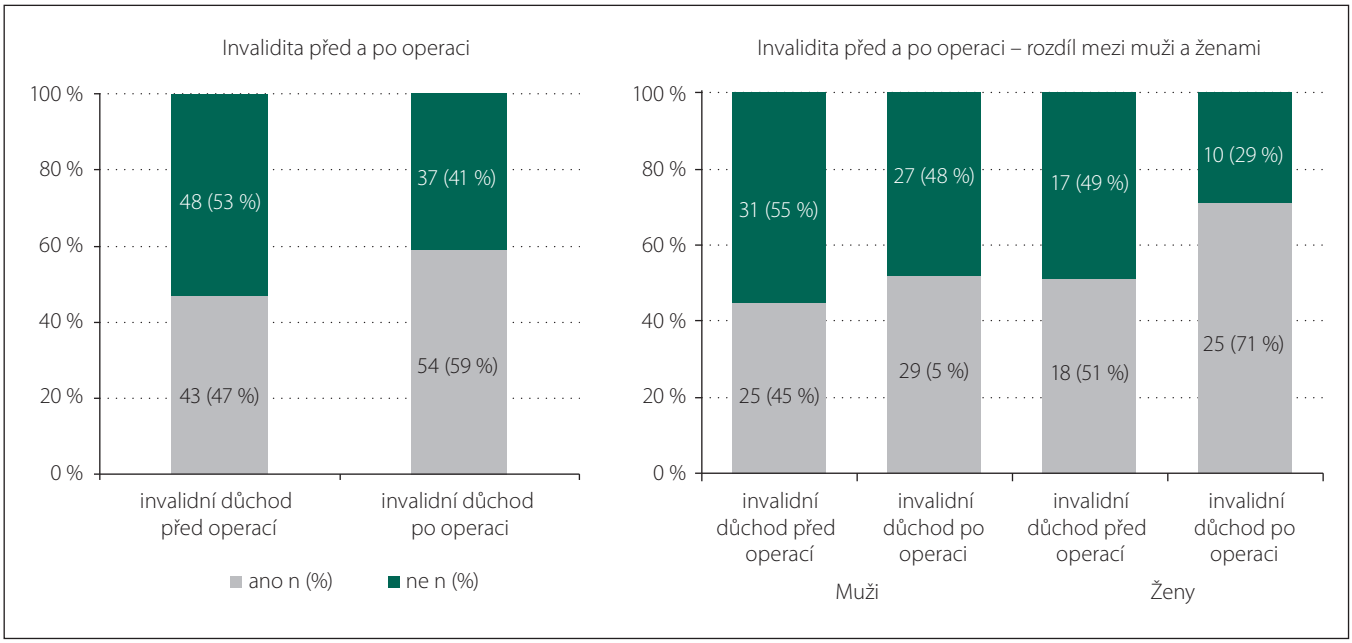
Pohlaví	muž n (%)	56 (62)
	žena n (%)	35 (39)
Věk v době operace	18–25 let n (%)	6 (7 %)
	26–35 let n (%)	22 (24 %)
	36–45 let n (%)	32 (35 %)
	46–60 let n (%)	30 (33 %)
	více než 61 let n (%)	1 (1 %)
Nejvyšší dosažené vzdělání	základní n (%)	11 (12 %)
	učební obor bez maturity n (%)	49 (50 %)
	středoškolské s maturitou n (%)	23 (25 %)
	vyšší odborné nebo vysokoškolské n (%)	12 (10 %)
Vznik epilepsie	do 1 roku věku n (%)	9 (10 %)
	1–10 let n (%)	32 (35 %)
	11–18 let n (%)	25 (27 %)
	19–64 let n (%)	25 (27 %)
	nad 65 let n (%)	0 (0 %)
Doba od operace	více než 1 rok	8 (9 %)
	více než 2 roky	25 (27 %)
	více než 5 let	31 (34 %)
	více než 10 let	27 (30 %)
Výsledky chirurgické léčby – vymizení epileptických záchvatů	ano	58 (64 %)
	je jich méně	25 (27 %)
	ne	6 (7 %)



Graf 1. Změny v zaměstnanosti před a po operaci.

Graf 1a) Hodnoceny změny v zaměstnanosti před a po operaci bez ohledu na pohlaví respondentů.

Graf 1b) Hodnoceny změny v zaměstnanosti před a po operaci z hlediska pohlaví respondentů.



Graf 2. Změny v invaliditě před a po operaci.
Graf 2a) Hodnoceny změny v invaliditě před a po operaci bez ohledu na pohlaví respondentů.
Graf 2b) Hodnoceny změny v invaliditě před a po operaci z hlediska pohlaví respondentů.

mělo základní vzdělání, 12 pacientů (13,2 %) mělo vzdělání vyšší odborné nebo vysokoškolské. Jak bylo uvedeno výše, u všech pacientů byl dodržen časový limit nejméně jednoho roku od operace, 33 pacientů (36,3 %) bylo méně než pět let po operaci, 31 (34,1 %) méně než 10 let od operace, zbylých 27 pacientů (29,7 %) bylo více než 10 let po operaci (tab. 1).

Výsledky chirurgické léčby – hodnoceno vymizení epileptických záchvatů

U 59 pacientů (64,8 %) vymizely úplně epileptické záchvaty po operaci, u dalších 26 (28,5 %) se frekvence záchvatů výrazným způsobem snížila, u šesti pacientů (6,6 %) nedošlo k významné změně frekvence epileptických záchvatů (tab. 1). Je zajímavé, že ze skupiny pacientů, u kterých došlo k úplnému vymizení záchvatů, si 20 (33,9 %) stěžovalo na jiné obtíže. Část pacientů udávala obtíže, které jsou v přímé souvislosti s operačním výkonem, konkrétně poruchy zorného pole (šest pacientů (6,6 %)), vznik pooperační hemiparézy (dva pacienti (2,2 %)), či poruchy paměti (tři pacienti (3,3 %)). Druhá skupina pacientů udávala obtíže, o jejichž kauzálním vztahu k operaci můžeme spíše debatovat. Nejčastěji se jednalo o bolesti hlavy (šest pacientů (6,6 %)), ojediněle (méně než u tří pacientů v celém souboru) byly přítomny psychické problémy, poruchy sluchu a spánku, vyšší únavnost.

Dopady chirurgické léčby epilepsie na jednotlivé aspekty života po operaci

Zaměstnanost, invalidita, držení řidičského oprávnění

Před operací bylo zaměstnáno (v zaměstnaneckém poměru či jako osoba samostatně výdělečně činná (OSVČ)) celkem 46 (50,5 %) pacientů, po operaci došlo k mírnému vzestupu zaměstnanosti o čtyři pacienty (4,4 %), tedy po operaci bylo zaměstnáno 50 pacientů (54,9 %), tento rozdíl v zaměstnanosti nedosáhl statistické významnosti ($p = 0,596$) (graf 1a). Nárůst zaměstnanosti se týkal pouze mužů. Počet zaměstnaných mužů po operaci vzrostl z 31 (55,4 %) na 37 (66,1 %), tj. o 10,7 %, ani zde však nebyl rozdíl statisticky signifikantní ($p = 0,264$). Upozorňujeme však na důležitou skutečnost, že po operaci našlo nově zaměstnání 13 mužů, avšak sedm mužů z nejrůznějších důvodů pracovat přestalo, došlo tedy k celkovému vzestupu zaměstnanosti o šest mužů. U žen naopak došlo k mírnému poklesu zaměstnanosti po operaci, před operací bylo zaměstnáno 15 žen (42,9 %), po operaci pak pouze 13 (37,1 %) ($p = 0,773$) (graf 1b). I zde zdůrazňujeme fakt, že po operaci nově našlo zaměstnání pět žen, ale sedm žen po operaci pracovat přestalo, došlo tedy k celkovému poklesu zaměstnanosti o dvě ženy.

Před operací mělo invalidní důchod 43 pacientů (47,3 %), po operaci vzrostl jejich počet na 54 (59,3 %), tento vzestup však nebyl statisticky významný ($p = 0,054$) (graf 2a). Nově invalidní důchod získalo 19 pacientů, osm pacientů ale po operaci invalidní důchod ztratilo. Rovněž v „pobírání" invalidních důchodů byl přítomen rozdíl mezi jednotlivými pohlavími (graf 2b). U žen došlo k vzestupu v „pobírání" invalidního důchodu z 18 (51,4 %) na 25 (71,4 %), tento rozdíl dosáhl statistické významnosti ($p = 0,070$). U mužů nebyl tento nárůst tak významný, z 25 mužů (44,6 %) „pobírajících" invalidní důchod před operací vzrostl tento počet na 29 (51,8 %) ($p = 0,453$).

Vzhledem k faktu, že v našem souboru byli pouze pacienti s aktivní epilepsií, neměl nikdo před operací oprávnění k řízení motorových vozidel. Po operaci 19 pacientů (20,9 %) toto oprávnění získalo, což je statisticky významný nárůst ($p < 0,001$).

V další analýze jsme se pokusili určit jednotlivé proměnné, které souvisí se zaměstnaností pacienta po operaci (tab. 2). Byl zjištěn statisticky významný vztah mezi zaměstnáním po operaci a následujícími charakteristikami pacientů: pohlaví ($p = 0,009$), vzdělání ($p = 0,020$), zaměstnání před operací ($p = 0,006$), pobírání důchodu před ope-

rací (p = 0,021), pobírání důchodů po operaci (p = 0,001), získání řidičského oprávnění po operaci (p = 0,004). Následně byla provedena jednorozměrná logistická regrese, která hodnotila vliv jednotlivých charakteristik pacienta na zaměstnání po operaci (v logistické regresi byly použity pouze proměnné, které popisují stav pacienta před operací) (tab. 3). Pomocí výsledků získaných jednorozměrnou logistickou regresí byl vytvořen finální model, jehož cílem se predikce zaměstnání po operaci. Na základě tohoto modelu můžeme říci, že po operaci byli častěji zaměstnáni pacienti s vyšším než základním vzděláním (OR = 6,5; IS = 1,2–36,0; p = 0,033), muži než ženy (OR = 3,3; IS = 1,3–8,6; p = 0,013), pacienti, kteří měli zaměstnání již před operací (OR = 3,0; IS = 1,2–7,5; p = 0,021).

Kvalita života po operaci

Poslední část našeho dotazníku se věnovala subjektivnímu hodnocení kvality života po operaci. Polovina, 49 pacientů (53,8 %), udává pooperačně vzestup kvality života, což je statisticky významný rozdíl proti kvalitě života před operací. V další analýze jsme hledali faktory, které souvisí se změnou kvality života po operaci (tab. 4). Jediná proměnná, konkrétně zaměstnání po operaci, vykazuje statisticky významný vztah s kvalitou života po operaci. Z celkového počtu 50 pacientů, kteří jsou po operaci zaměstnáni, jich 32 (64,0 %) udává, že mají po operaci zlepšenou kvalitu života. Naopak z celkového počtu 41 pacientů, kteří po operaci nepracují, udává zlepšenou kvalitu života pouze 17 (41,5 %) pacientů (p = 0,037). Na základě údajů, které byly o pacientech známy před provedením operace, jsme se pokusili sestavit model logistické regrese, který by predikoval, zda bude mít pacient po operaci zlepšenou kvalitu života (tab. 5). Vzhledem k faktu, že se nám nepodařilo při použití jednorozměrné logistické regrese identifikovat charakteristiky pacientů, které by vysvětlovaly zlepšení života po operaci, nebylo možné sestavit smysluplný vícerozměrný logistický model.

Poslední otázka našeho dotazníku zněla: „Představte si, že byste mohl/mohla vrátit čas. Nechal/nechala byste se znovu operovat?" Většina, 78 (85,7 %) pacientů, odpověděla, že ano, 13 (14 %) odpovědělo ne. Dvě proměnné, konkrétně stupeň dosaženého vzdělání a kvalita života po operaci, vykazovaly statisticky významný vztah k odpovědi na tuto otázku (tab. 6). Většina, konkrétně 71 (88,8 %) z celkového počtu 80 pacientů s vyšším vzděláním než základním, by se nechala operovat znovu, naopak pouze sedm (63,6 %) z celkového počtu 11 pacientů se základním vzděláním by znovu podstoupilo operační výkon (p = 0,048). Čtyřicet devět pacientů (100,0 %), u kterých došlo ke zvýšení kvality života po operaci, by se nechalo operovat znovu. „Pouze" 29 ze 42 pacientů (69,1 %), u kterých po operaci nedošlo ke zvýšení kvality života, by opětovně podstoupilo operaci (p < 0,001). Rovněž i u této otázky jsme se pokoušeli najít pomocí jed-

Tab. 2. Zaměstnanost po operaci – vztah k ostatním proměnným.

		53 % zaměstnání po operaci		
		ano n (%)	ne n (%)	p hodnota
Věk v době operace	18–25 let	3 (50 %)	3 (50 %)	0,885
	26–35 let	12 (54,5 %)	10 (45,5 %)	
	36–45 let	19 (59 %)	13 (41)	
	46–60 let	16 (53 %)	14 (47)	
	více než 60 let	0 (0 %)	1 (100 %)	
Pohlaví	muž	37 (66 %)	19 (34 %)	**0,009**
	žena	13 (37 %)	22 (63 %)	
Vzdělání	základní	2 (18 %)	9 (82 %)	**0,020**
	středoškolské a vyšší	48 (60 %)	32 (40 %)	
Vznik epilepsie	v dětství (< 10 let věku)	26 (63 %)	15 (37 %)	0,278
	v dospívání (< 18 let věku)	11 (44 %)	14 (56 %)	
	v dospělosti (> 18 let)	13 (52 %)	12 (48 %)	
Zaměstnání před operací	ano	32 (70 %)	14 (30 %)	**0,006**
	ne	18 (40 %)	27 (60 %)	
Důchod před operací	ano	18 (42 %)	25 (58 %)	**0,021**
	ne	32 (67 %)	16 (33 %)	
Důchod po operaci	ano	18 (42 %)	25 (58 %)	**0,001**
	ne	18 (40 %)	27 (60 %)	
Záchvaty po operaci	přetrvávají	18 (56 %)	14 (44 %)	1,000
	vymizely	32 (54)	27 (46 %)	
Řidičské oprávnění	ano	16 (84 %)	3 (16 %)	**0,004**
	ne	34 (47 %)	38 (53 %)	

Tab. 3. Vliv jednotlivých proměnných na zaměstnanost pacientů po operaci – jednorozměrná logistická regrese.

Prediktor	OR	IS (95%)	p hodnota
Věk	1,006	(0,962; 1,051)	0,791
Pohlaví (muž/žena)	3,296	(1,366; 7,953)	**0,008**
Vzdělání			
(střední a vyšší/základní)	8,625	(1,602; 46,447)	**0,012**
Vznik pilepsie e			
(dětství/dospělost)	1,600	(0,583; 4,392)	0,362
(dospívání/dospělost)	0,725	(0,238; 2,208)	0,572
Zaměstnání před operací (ano/ne)	3,429	(1,442; 8,152)	**0,005**
Důchod před operací (ne/ano)	2,778	(1,184; 6,517)	**0,019**

Tab. 4. Změna kvality života po operaci.

		kvalita života po operaci		
		zvýšená	jiná odpověď*	p hodnota
Věk v době operace	18–25 let n (%)	4 (67 %)	2 (33 %)	0,785
	26–35 let n (%)	13 (59 %)	9 (41 %)	
	36–45 let n (%)	15 (47 %)	17 (53 %)	
	46–60 let n (%)	16 (53 %)	14 (47 %)	
	> 60 let n (%)	1 (100 %)	0 (0 %)	
Pohlaví	muž n (%)	29 (52 %)	27 (48 %)	0,670
	žena n (%)	20 (57 %)	15 (43 %)	
Vzdělání	základní n (%)	4 (36 %)	7 (64 %)	0,334
	středoškolské a vyšší n (%)	45 (56 %)	35 (44 %)	
Vznik epilepsie	v dětství (< 10 let)	21 (51 %)	20 (49 %)	0,894
	v dospívání (< 18 let)	14 (56 %)	11 (44 %)	
	v dospělosti (> 18 let)	14 (56 %)	11 (44 %)	
Zaměstnání před operací	ano n (%)	26 (57 %)	20 (44 %)	0,676
	ne n (%)	23 (51 %)	22 (49 %)	
Důchod před operací	ano n (%)	22 (51 %)	21 (49 %)	0,677
	ne n (%)	27 (56 %)	21 (44 %)	
Zaměstnání po operaci	ano n (%)	32 (64 %)	18 (36 %)	**0,037**
	ne n (%)	17 (41,5 %)	24 (58,5 %)	
Důchod po operaci	ano n (%)	25 (46 %)	29 (54 %)	0,091
	ne n (%)	24 (65 %)	13 (35 %)	
Záchvaty po operaci	přetrvávají n (%)	14 (44 %)	18 (56 %)	0,189
	vymizely n (%)	35 (59 %)	24 (41 %)	
Řidičské oprávnění po operaci	ano n (%)	12 (62 %)	7 (37 %)	0,442
	ne n (%)	37 (51 %)	35 (49 %)	

* snížená, stejná, nevím.

Tab. 5. Vliv jednotlivých proměnných na kvalitu života po operaci – jednorozměrná logistická regrese.

Prediktor	OR	IS (95%)	p hodnota
Věk	0,992	(0,949; 1,037)	0,713
Pohlaví (muž/žena)	0,806	(0,344; 1,885)	0,618
Vzdělání			
(středoškolské a vyšší/základní)	3,354	(0,817; 13,778)	0,093
Vznik pilepsie e			
(dětství/dospělost)	0,825	(0,304; 2,241)	0,706
(dospívání/dospělost)	1,000	(0,327; 3,055)	1,000
Zaměstnání před operací (ano/ne)	1,243	(0,545; 2,839)	0,605
Důchod před operací (ano/ne)	1,227	(0,573; 2,804)	0,627

norozměrné logistické regrese faktory, které by mohly předoperačně predikovat odpověď na tuto otázku (tab. 7). Významným faktorem bylo pouze vzdělání (OR = 9,4; IS = 1,4–61,9; p = 0,020), proto vícerozměrný model nebyl sestavován.

Diskuze

Pacientům s farmakorezistentní epilepsií by dle doporučení ILAE měla být nabídnuta možnost operačního řešení tohoto onemocnění [8]. „Klasickým" a všeobecně akceptovaným měřítkem úspěšnosti operační léčby je vymizení epileptických záchvatů, avšak v současnosti se naše pozornost stále více soustřeďuje i na jiné cíle, které v běžném životě člověka hrají neméně důležitou roli. V naší práci se detailněji věnujeme problematice zaměstnanosti a kvalitě života, ale podobný význam hraje i možnost většího zapojení se do společenského dění, lepší přístup ke vzdělání či získání větší samostatnosti a nezávislosti.

Jak bylo uvedeno výše, „klasickým" měřítkem úspěšnosti chirurgické léčby epilepsie je dosažení bezzáchvatovosti, čehož se nám podařilo dosáhnout u 64,8 % pacientů z našeho souboru (jednalo se o neselektovanou skupinu pacientů jak s temporální, tak extratemporální epilepsií, u níž je obecně horší prognóza). Toto číslo dobře koresponduje s výsledky publikovanými Wiebem et al, kteří prokázali efektivitu chirurgické léčby u pacientů s temporální epilepsií v rámci randomizované kontrolované klinické studie [9]. Ve své práci náhodně rozdělili 80 pacientů s farmakorezistentní temporální epilepsií na pacienty, kteří podstoupili chirurgickou léčbu, a na pacienty, kteří byli ponecháni „pouze" na léčbě farmakologické. Po operaci bylo bez záchvatů 58 % pacientů, ze skupiny konzervativně léčených pacientů to bylo jen 8 %.

První oblastí, kterou jsme hodnotili v našem dotazníku, byla otázka zaměstnanosti pacientů před operací a po ní. V rámci naší studie došlo pouze k minimálnímu vzestupu zaměstnanosti po operaci, před operací bylo zaměstnáno 50 % pacientů, po operaci 55 %, tj. zaměstnanost se zvýšila o 5 %. V zahraniční literatuře jsou přítomny diskrepance při hodnocení zaměstnanosti pacientů po epileptochirurgickém výkonu. Existují práce, které dokumentují jak její nárůst, tak i její pokles [10–12]. Ve studii publikované Zarrolim et al, která analyzovala změnu zaměstnanosti u cca 350 pacientů s temporální epilepsií, došlo k nárůstu zaměstnanosti po operaci o 16 %, před operací nemělo zaměstnání 41 % pacientů, po operaci se počet nezaměstnaných snížil na 25% [10]. Ve studii publikované Lendtem et al došlo k poklesu v nezaměstnanosti o 16 % [11]. Naopak v práci Reevse et al došlo k poklesu zaměstnanosti po operaci o 3 % [12]. Dle na-

šeho názoru mohou být tyto rozdíly podmíněny mnoha faktory: rozdílnými společenskými a sociálními systémy v jednotlivých státech, rozdílným výběrem pacientů a rovněž rozdílným designem jednotlivých studií. Zde bychom rádi vyzvedli jeden, ač na první pohled nepatrný, avšak v rámci hodnocení zaměstnanosti pacientů po operaci důležitý faktor – dobu od operace. My jsme zařadili do naší studie již pacienty jeden rok po operaci, ale například Lendt et al hodnotili pacienty až čtyři roky po operaci [11]. Je pravděpodobné, že rok od operace je příliš krátká doba, aby se pacient přizpůsobil nový nárokům, které jsou na něj kladeny v souvislosti s hledáním zaměstnání. Pacient, který podstoupil operaci před čtyřmi roky, měl delší čas k adaptaci na změnu života a na změnu svého společenského postavení, což není změna, kterou je člověk schopen učinit ze dne na den. Jedná se bezesporu o dlouhodobější proces, při kterém je nutné si osvojit kompletně nový soubor návyků a přístupů. Pokud bychom tedy měli hodnotit dopad chirurgické léčby na zaměstnanost pacientů, bylo by vhodnější zvolit delší minimální časový interval pro validitu hodnocení.

Naše studie zaznamenala nárůst počtu pacientů pobírajících invalidní důchod po operaci ve srovnání s předoperačním obdobím o 12 %, tento nárůst však nedosáhl statistické významnosti. Obdobný trend byl zdokumentován rovněž ve Švédsku, kde počet pacientů s invalidním důchodem vzrostl o 7 % v prvních dvou letech po operaci, ve třetím roce dokonce až o 10 % [13].

V rámci naší analýzy jsme identifikovali faktory, které souvisí se zaměstnaností po operaci. Jedná se o následující demografická data a charakteristiky pacientů: zaměstnanost před operací (pacienti, kteří mají zaměstnání před operací, jsou častěji zaměstnaní i po operaci), pohlaví (muži jsou zaměstnáni častěji než ženy), vzdělání (pacienti s vyšším vzděláním jsou zaměstnáni častěji), přiznaná invalidita před operací a po ní (pacienti s přiznaným důchodem jsou zaměstnáni méně často). Se zaměstnáním po operaci souvisí i držení řidičského oprávnění.

Obdobné faktory ovlivňující zaměstnanost po operaci, přestože se jedná o odlišné socio-ekonomické prostředí (Spojené státy americké vs. Česká a Slovenská republika), identifikovali Zarroli et al [10]. Dle jejich výsledků bylo zaměstnání před operací významným prediktorem zaměstnání po operaci a stejně jako v naší studii část žen, která

Tab. 6. Odpověď, na otázku: „Představte si, že byste mohl/mohla vrátit čas. Nechal/nechala byste se znovu operovat?“.

		„Nechal/a byste se znovu operovat?“		
		Ano, nechal/a.	Ne, nenechal/a.	p hodnota
Věk v době operace	18–25 let n (%)	5 (83 %)	1 (17 %)	1,000
	26–35 let n (%)	19 (86 %)	3 (14 %)	
	36–45 let n (%)	27 (84 %)	5 (16 %)	
	46–60 let n (%)	26 (87 %)	4 (13 %)	
	> 60 let n (%)	1 (100 %)	0 (0 %)	
Pohlaví	muž n (%)	48 (86 %)	8(14 %)	1,000
	žena n (%)	30 (85,7 %)	5 (14 %)	
Vzdělání	základní n(%)	7 (64 %)	4 (36 %)	**0,048**
	středoškolské a vyšší n (%)	71 (89 %)	9 (11 %)	
Vznik epilepsie	v dětství (< 10 let)	34 (83 %)	7 (17 %)	0,192
	v dospívání (< 18 let)	20 (80 %)	5 (20 %)	
	v dospělosti (> 18 let)	24 (96 %)	1 (4 %)	
Zaměstnání před operací	ano n (%)	42 (91 %)	4 (9 %)	0,145
	ne n (%)	36 (80 %)	9 (20 %)	
Důchod před operací	ano n (%)	36 (83 %)	9 (16 %)	0,766
	ne n (%)	42 (88 %)	6 (13 %)	
Zaměstnání po operaci	ano n (%)	45 (90 %)	5 (10 %)	0,237
	ne n (%)	33 (80,5 %)	8 (19,5 %)	
Důchod po operaci	ano n (%)	45 (83 %)	9 (17 %)	0,549
	ne n (%)	33 (89 %)	4 (11 %)	
Záchvaty po operaci	přetrvávají n (%)	26 (81 %)	6 (19 %)	0,369
	vymizely n (%)	33 (89 %)	4 (11 %)	
Řidičské oprávnění po operaci	ano n (%)	19 (100 %)	0 (0 %)	0,063
	ne n (%)	59 (82 %)	13 (18 %)	
Kvalita života po operaci	zvýšená	49 (100 %)	0 (0 %)	< 0,001
	jiná odpověď	29 (69 %)	13 (31 %)	

Tab. 7. Vliv jednotlivých proměnných na odpověď na otázku „Nechal/a byste se operovat znovu?“ – jednorozměrná logistická regrese.

Prediktor	OR	IS (95%)	p hodnota
Věk	1,008	(0,947; 1,073)	0,807
Pohlaví (muž/žena)	1,000	(0,299; 3,343)	1,000
Vzdělání			
(středoškolské a vyšší/základní)	9,429	(1,434; 61,986)	**0,020**
Vznik pilepsie e			
(dětství/dospělost)	0,202	(0,023; 1,754)	0,147
(dospívání/dospělost)	0,167	(0,018; 1,546)	0,115
Zaměstnání před operací (ano/ne)	2,625	(0,745; 9,246)	0,133
Důchod před operací (ano/ne)	1,361	(0,419; 4,420)	0,608

byla před operací zaměstnána, zaměstnání po operaci ztratila (v práci Zarroli et al je však přítomen celkový nárůst zaměstnanosti i u žen). Výše uvedená ztráta zaměstnání byla odůvodněna faktem, že se část žen po operaci rozhodla zůstat trvale v domácnosti a věnovat se péči o rodinu a děti. Předpokládáme, že obdobná tendence je přítomna i v rámci České a Slovenské republiky.

Pobírání invalidního důchodu či státní podpory (dle zvyklostí jednotlivých zemí) je v literatuře asociováno s nižší zaměstnaností po operaci [14,15]. Částečně je toto zcela jistě podmíněno faktem, že pacienti pobírající invalidní důchod mohou mít výraznější kognitivní a psychické obtíže v souvislosti s epilepsií, mohou rovněž trpět významnějšími somatickými onemocněními bez jednoznačného vztahu k epilepsii. Může se však projevovat i snížená motivace této skupiny pacientů najít zaměstnaní.

Dalším faktorem, který má vztah k zaměstnání pacientů po operaci, je získání řidičského oprávnění (jedná se o řidičské oprávnění pouze pro osobní účely, nikoliv o řidičské oprávnění, které umožňuje řízení motorových vozidel v pracovněprávním vztahu). Po operaci získalo řidičské oprávnění jen 20,9 % pacientů, z nichž však bylo po operaci zaměstnáno 84,2 %. Z pacientů, kteří řidičské oprávnění nezískali, bylo po operaci zaměstnáno jen 47,2 %. Výše uvedený vztah byl potvrzen celou řadou zahraničních studií. Řidičské oprávnění se ukazuje jako nezávislý prediktor zaměstnanosti pacientů i v modelech, v nichž byl statisticky odstraněn vliv případné mentální retardace, psychických či somatických komorbidit [12,16]. V literatuře se objevují názory, že řidičské oprávnění, ač jen pro osobní účely, ulehčuje pacientům hledání zaměstnání, pacienti s řidičským oprávněním jsou snáze schopni dorazit na pracovní pohovor, případně i do práce, nemusí se spoléhat na veřejné dopravní prostředky, na pomoc rodiny či blízkých. Objevují se rovněž spekulace, že pacienti, kteří po operaci získají řidičské oprávnění, disponují povahovými rysy, které jim usnadňují hledání zaměstnání, zvláště je vyzdvihována jejich ochota riskovat a čelit případnému zklamání, ochota učit se novým věcem. Tyto spekulace nelze potvrdit ani vyvrátit výsledky této či jiné studie.

Bylo pro nás překvapivé, že jsme nepotvrdili vztah zaměstnanosti po operaci a některých dalších faktorů, které jsou často přítomny v ostatních studiích. Prvním takovýmto vztahem je vztah zaměstnanosti po operaci a vymizení epileptických záchvatů [10,17–22]. V rámci naší práce bylo zaměstnáno 56,3 % pacientů, u kterých záchvaty vymizely, a 54,2 % pacientů, u kterých záchvaty po operaci přetrvávaly. Dle Zarroli et al je právě úplné vymizení či velmi podstatná redukce záchvatů nejdůležitějším faktorem, který určuje, zda bude po operaci pacient zaměstnán či nikoliv [10]. Právě pacienti, u kterých dojde po operaci k úplnému vymizení či podstatné redukci záchvatů, nachází častěji práci než pacienti, u kterých dochází k méně významné změně frekvence záchvatů. Obdobný vztah je přítomen i v mnoha dalších publikacích. Další faktor ovlivňující zaměstnanost pacientů, jež se v naší studii nepodařilo potvrdit, byl věk pacienta v době operace [18,23,24]. Mladší pacienti mají dle výsledků jiných publikací lepší šanci najít zaměstnání. Ve studii Sperlinga et al z poloviny 90. let minulého století byl průměrný věk pacienta, kterému se po operaci podařilo najít zaměstnání 31,0 ± 8 let. Naopak průměrný věk pacienta, který po operaci zaměstnání nenašel, byl 42,4 ± 10,9 let [18]. Obdobné výsledky v roce 2009 publikovali i George et al [23]. Výše popsaný jev je pravděpodobně podmíněn částečně společensky (mladší lidé obecně hledají snáze zaměstnaní), ale částečně to souvisí jistě i se schopností mladších pacientů se snáze učit novým věcem a přizpůsobovat se více nárokům. Naopak starší pacienti se již mohli vžít a osvojit si „roli nemocného" [25]. Otázkou je, proč jsme v naší skupině nenašli ani věk v době operace, ani vymizení záchvatů jako důležitý prediktor pro vyšší zaměstnanost pooperačně. Opětovně se domníváme, že by bylo potřeba delšího časového odstupu od operace. Navíc nejsme v našich modelech schopni provést korekci ani na somatické a psychiatrické komorbidity, roli zde samozřejmě může hrát i sociální prostředí a velikost jednotlivých souborů.

Zaznamenali jsme významný nárůst kvality života po operaci: 53,8 % pacientů udávalo, že se jejich kvalita života po operaci zvýšila. Tento výsledek odpovídá výsledkům většiny studií, které se zabývaly touto problematikou. Metaanalýza publikovaná Seiamem et al v roce 2011 analyzovala výsledky 39 publikací, které se věnovaly změně kvality života u pacientů s epilepsií [26]. Většina prací, konkrétně 36 (92,3 %), našla po operaci zvýšenou kvalitu života. Zbylé tři práce (7,7 %) nezaznamenaly po operaci zvýšení kvality života [27–29]. Z našeho pohledu je významné srovnání s českou prací Preisse a Vojtěcha, kteří se zabývali změnou kvality života po operaci u 50 pacientů s farmakorezistentní, většinou temporální epilepsií, operovaných v nemocnici Na Homolce. Tito autoři našli rovněž významné zvýšení kvality života, zvláště v následujících sférách: percepce zdraví, sociální funkce a strach ze záchvatu [30].

V naší studii byla přítomna pouze jediná proměnná – zaměstnání pacienta po operaci – která statisticky korelovala se zvýšením kvality života po operaci. Z celkového počtu 50 pacientů, kteří měli po operaci zaměstnání, udávalo zlepšení kvality života 64,0 %. Z počtu 41 pacientů, kteří po operaci zaměstnání neměli, uvádělo zlepšení kvality života pouze 41,5 %. Obdobná korelace mezi kvalitou života po operaci a zaměstnáním po operaci byla nalezena i v několika dalších studiích [31–34]. Byla popsána celá řada proměnných, které souvisí s kvalitou života po operaci. Z údajů, které jsou známy již před vlastní operací, kvalitu života po operaci ovlivňují následující: psychologické a psychiatrické komorbidity (přítomnost psychiatrických onemocnění, špatná výkonnost v psychologických testech), nerealistická očekávání od operace, očekávání, která nebyla po operaci naplněna [31,35,36]. Z pooperačních faktorů ovlivňuje kvalitu života především dosažená dobrá kompenzace záchvatů [26]. Zdá se však, že úplné vymizení epileptických záchvatů je pro kvalitu života pacienta mnohem důležitější než pouhá jejich redukce. Dalším faktorem zvyšujícím kvalitu života pacienta je držení řidičského oprávnění [34]. Naopak kvalitu života po operaci snižovala přítomnost nežádoucích účinků antiepileptické medikace, psychické obtíže, obtíže s verbální pamětí, těžký průběh záchvatů, přítomnost jiného somatického onemocnění [32–34,37–39]. Je pro nás překvapením, že se vymizení epileptických záchvatů v naší práci neuplatňovalo jako faktor, který by ovlivňoval kvalitu života po operaci. V naší studii udávalo zvýšenou kvalitu života 59,3 % pacientů, kteří po operaci záchvaty neměli, a 43,8 % pacientů, u kterých epileptické záchvaty přetrvávaly i po operaci. Můžeme se domnívat, že je tento jev částečně podmíněn jinými zdravotními obtížemi, jež pacienti popisovali v našem dotazníku. Druhým možným vysvětlením je „syndrom břemene normality" (burden of normality syndrome) popsaný Wilsonovou v roce 2001 [40]. „Syndrom břemene normality" se vyskytuje u pacientů po vyléčení z ja-

kéhokoliv závažného chronického onemocnění (týká se pacientů po transplantacích, onkologických pacientů, pacientů s kardiovaskulárním onemocněním). Pacienti a jejich rodiny, ač vyléčeni z chronického onemocnění, nejsou s výsledky léčby spokojeni. Pacienti si stěžují, že jim léčba nic pozitivního nepřinesla, a v některých případech dokonce litují, že léčbu podstoupili, přestože vedla k jejich uzdravení. Známky „syndromu břemene normality" nalézáme v různém stupni až u 66 % pacientů v prvních dvou letech po epileptochirurgickém výkonu. Klinicky se může manifestovat psychickými obtížemi (nadměrné očekávání od sebe i od ostatních, lítost nad předchozím životem s nemocí), změnami behaviorálními (nadměrná denní aktivita ve snaze „dohnat vše zameškané" nebo naopak stažení se do sebe, snížení aktivity) a sociálními (narušení vztahu s rodinou, partnerem, přáteli, obtíže s hledáním zaměstnání) [25,30,40]. Častěji se setkáváme se „syndromem tíhy normality" u pacientů, kteří mají s léčbou spojeny nerealistická očekávání (vyřešení sociálních a rodinných problémů, zvýšení inteligence) než u pacientů, kteří chtějí operací dosáhnout realistických, dobře definovaných cílů (vymizení epileptických záchvatů, získání řidičského oprávnění).

Poslední otázka v našem dotazníku byla hypotetická, dotazovala se pacienta, zda by se nechal znovu operovat, kdyby mohl vrátit čas. Naprostá většina pacientů, konkrétně 85,7 %, odpovědělo, že by operaci podstoupilo znovu. Tuto hodnotu považujeme za srovnatelnou s výsledky publikovanými z Mayo kliniky v Rochesteru, kde by 85 % pacientů podstoupilo epileptochirurgickou léčbu [41]. Operaci by znovu podstoupili všichni pacienti, kteří po operaci udávají zlepšení kvality života.

Uvědomujeme si četné limitace naší studie. Jedná se o relativně malý počet respondentů, pacienti byli dotazováni v různém časovém intervalu od operačního výkonu. Jak bylo zmíněno již v úvodu, nebyl použit standardizovaný dotazník, což sice umožnilo získání odpovědí zcela anonymní formou (při dotazování nebyl přítomen ani lékař, ani psycholog, jehož postoj a pohled na chirurgii epilepsie by mohl ovlivňovat odpovědi pacienta), na druhé straně neumožňuje zcela přesné srovnání s výsledky ostatních prací. Přes všechny výše zmíněné nedostatky si myslíme, že je tato práce schopna reflektovat vztah našich pacientů k epileptochirurgické léčbě a benefity, které jim může tato léčba nabídnout.

Závěr

Pacienti s farmakorezistentní epilepsií vytváří různorodou skupinu, u které by měla být posouzena možnost operační léčby. Operace nabízí pacientovi vyšší pravděpodobnost zbavení se epileptických záchvatů ve srovnání s léčbou farmakologickou. Po operaci stojí pacient před celou řadou dalších problémů a úskalí, dochází k významné změně jeho životní role z „nemocného" člověka na člověka „zdravého", na něhož jsou kladeny vyšší nároky. Na základě našeho dotazníkového šetření můžeme říci, že ač velká část pacientů podstoupila úspěšný epileptochirurgický výkon, který je zcela zbavil záchvatů, zaměstnání se podařilo najít jen malé části z nich. Je zde vidět prostor pro aktivitu sociálních pracovníků, pro rekvalifikační programy, pro programy zvyšování kvalifikace či programy motivace zaměstnavatelů, které by umožnily lepší zapojení našich bývalých pacientů do pracovního procesu. I přes tyto nedostatky „následné rehabilitace" je epileptochirurgická léčba ze strany našich operantů hodnocena kladně, přináší jim v naprosté většině případů zvýšení kvality života a většina z nich by znovu podstoupila operační zákrok.

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