

**Preoperative Examination of Temporal Lobe Epilepsy:
Determination of New Lateralisation Signs and Prognostic
Factors**

PhD Thesis

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Abbreviations

aTLR: apical temporal lobe resection

CI: confidence interval

DNET: dysembryoplastic neuroepithelial tumor

EEG: electroencephalography

ATLR: anterior temporal lobe resection

EZ: epileptogenic zone

FLAIR: „fluid attenuated inversion recovery” sequence

FLIRT: FMRIB's Linear Image Registration Tool

FIRST: FMRIB's Integrated Registration and Segmentation Tool

FSL: FMRIB Software Library

GTCS: generalised tonic-clonic seizure

HS: hippocampal sclerosis

IEP: interictal epileptiform potentials

MPRAGE: magnetization-prepared rapid gradient-echo imaging

mTLE- HS: mesial temporal lobe epilepsy with hippocampal sclerosis

OR: odds ratio

PMS: psychomotor seizure

SMA: supplementary motor area

SWI: susceptibility weighted imaging

TLE: temporal lobe epilepsy

TLE-HS: temporal lobe epilepsy with hippocampal sclerosis

TLR: temporal lobe resection

PIV: pure ictal vocalisation

TOF: time of flight 3D angiography

Introduction and objectives

Approximately 0.5-1% of the population suffers from epilepsy. Temporal lobe epilepsy (TLE) accounts for nearly 30% of all epilepsies and 50-60% of the most common, adulthood epilepsy. According to the classical approach, TLE is a symptomatic, focal epilepsy and can be further divided into mesial and lateral (neocortical) forms within the temporal lobe, based on its localisation. Although, the latest epilepsy classification of the International League Against Epilepsy (ILAE) does not make such a differentiation and defines only 'mesial temporal lobe epilepsy with hippocampal sclerosis' (mTLE-HS) as a separate epilepsy syndrome, thinking in terms of mesial/lateral entities still continues to have clinical significance. About 80% of mesial temporal lobe epilepsies with hippocampal sclerosis (mTLE-HS) is accompanied by HS. Neoplasms or cortical developmental abnormalities are often in the background of neocortical TLE. In about half the cases TLE is well-manageable with pharmacotherapy. However, if the first or second anti-epileptic medication therapy fails to achieve a seizure-free status, further modifications or combinations of the medication are unlikely to prove successful. In such cases, epilepsy surgery examinations are mandated; the first critical step is the selection of patients that is, it is indicated in the case of all patients who have proven pharmacoresistant and where epilepsy surgery as a possible solution arises based on available imaging and electro-clinical examination results. The prior aim of resective epilepsy surgeries is the removal or disconnection of the cortex responsible for seizure generation, i.e. the epileptogenic zone (EZ), obviously, with the preservation of the eloquent cortex, thereby preventing the postoperative deterioration of sensomotor and cognitive functions (speech, memory). TLE is well-treatable with surgery, the most common intervention being anterior temporal lobe resection (ATLR), with 60-80% of patients seizure-free one year after surgery. A randomised study comparing the treatment of TLE with medication or surgery clearly highlighted the greater efficacy of the surgical solution. The present thesis intends to answer three questions in connection with the improvement of the efficiency of pre-operative examinations and the selection of patients for surgery:

1. Determination of the incidence and lateralisation value of ictal vocalisation in temporal lobe epilepsy.
2. Examination of preoperative surgical prognostic factors in amygdalar epilepsy.
3. The use of R2* relaxometry in determining the epileptogenic zone during surgical examination of temporal lobe epilepsy.

1. Determination of the incidence and lateralisation value of ictal vocalisation in temporal lobe epilepsy

Looking at international literature, only one study investigated the lateralisation value of ictal vocalisation in TLE (Gabr et al., 1989), according to which, it occurred more frequently in patients having a dominant focus than in non-dominant TLE (62% vs. 37%). This result, however, was not significant most probably due to the low patient number (n=35) (Gabr et al., 1989).

1.1. Methods

We evaluated video-EEG recordings of 184 patients who had undergone presurgical evaluation in epilepsy centres in Pécs and Bielefeld. Only those patients were enrolled in the study who had had video-recorded psychomotor seizure (PMS) and had undergone epilepsy surgery subsequent to monitoring. Inclusion criteria were the following:

(1) Age above 16 years (2) the presence of pharmacoresistant TLE with PMS (3) unilateral temporal epileptogenic lesion (4) prolonged video-EEG monitoring with ictal video-EEG recording (5) preoperative high-resolution MRI (6) successful epilepsy surgery between 1996 – 2005 (>1 year postoperative seizure-free period). Inclusion criteria were met by 97 patients (49 females; mean age was 33.2±11 years; mean age at onset of epilepsy was 12.8 years). Audiovisual recordings of these patients' seizures were re-analysed. Seventy-eight patients were suffering from mesial and 19 from lateral TLE. The localisation of the epileptogenic focus was determined based on the position of the surgically removed temporal lobe lesion. Speech dominance had to be determined in 57 patients: in 46 cases the Wada-test, in 11 cases, functional MRI was performed. Out of the 97 patients, 44 had surgery on the left-side, 53 on the right side. In order to re-analyse seizure recordings, 1-3 subsequent recordings were chosen for each patient. Exclusively PMSs were analysed, 223 in total. **Pure ictal vocalisation (PIV)** was defined according to a previous study (Janszky et al., 2000b), which defines an uttered sound as PIV if it is apparently an ictal phenomenon, if it does not go for speech and is not accompanied by apnoea, generalised tonic-clonic seizure (GTCS) or a clonic seizure. We analysed the incidence of PIV and its connection to the epileptic focus and other clinical parameters.

1.2. Results

PIV occurred in 22 (23%) of patients with TLE out of the 97, while out of all observed seizures PIV occurred in 18% of the recordings. While 37% of PIV occurred in cases of left-

sided TLE, 11% in right-sided TLE ($p < 0.01$). There were no differences as to the occurrence of PIV with respect to sex, age and lateral/mesial TLE. The age at onset of epilepsy showed a correlation with the PIV phenomenon. PIV occurred primarily in those patients whose epilepsy started in their childhood (mean age at onset 8.7 ± 6 years), as opposed to non-PIV patients who had the onset at age 14.0 ± 9 ($p < 0.05$). Since age at onset correlated with the PIV phenomenon, we investigated whether this could be due to PIV occurring in the case of lesions developing at an early age. PIV occurred in 24% of patients with HS and in 20% of patients without HS ($p = 0.58$). There was no difference between the two patient groups regarding dysgenetic aetiology.

In the case of post-ictal aphasia, 36% of patients produced PIV, while in those without a post-seizure aphasia it was only 19% ($p < 0.05$). Out of 59 patients, whose speech dominance had been determined, PIV occurred in 37% of the cases with dominant TLE and in 14% of cases with non-dominant TLE ($p < 0.05$). As regards seizures, 30% of PIV occurred in the case of dominant-side seizures and 9% in seizures in the non-dominant side ($p < 0.01$). Logistic regression analysis was performed to determine, whether the three studied variables show significant correlation with PIV independent of each other (speech dominance, post-ictal aphasia, age at onset of epilepsy). The analysis revealed that both **hemispheric dominance** ($p = 0.05$), and **age at onset of epilepsy** ($p < 0.05$) showed a significant correlation independent of each other, post-ictal aphasia on the other hand, did not. In order to exclude hemispheric dominance as the main interfering factor in the examination of the relationship between age at onset of epilepsy and PIV, we subsequently considered only those patients with dominant TLE. If PIV occurred, the mean age at onset of epilepsy was 5.5 ± 3.6 years, whereas in cases without PIV it was 16.4 ± 9.4 years ($p < 0.01$).

1.3. Summary and interpretation of results

- (1) **PIV is a common phenomenon**, affecting one in every four patients with TLE.
- (2) **PIV is more common to accompany left-sided (dominant) TLE.**
- (3) PIV primarily occurs **in TLE with childhood onset.**

The present study revealed that PIV primarily occurred in dominant-side (left) TLE. Two related articles have been published previously: in an investigation carried out by Gabr and colleagues (1989) in patients with TLE with a dominant focus, ictal vocalisations were more common than in patients with a focus in the non-dominant hemisphere (62% vs. 37%), this tendency was not statistically significant. The lack of statistical significance, however, could

also be due to the small number of patients (35 patients were examined in total). Authors drew the direct conclusion that ictal vocalisation was unrelated to hemispheric lateralisation, although the left/right TLE ratio with respect to ictal vocalisation was nearly the same in Gabr's study as in ours, the only difference being the number of cases. We found a connection between the occurrence of PIV and early onset of epilepsy in TLE. An earlier study showed that TLE can be further divided on the basis of age at onset. Based on age at onset, we can differentiate childhood (peak of occurrence at age 5.5 years), teenage (peak of occurrence at age 15 years) and young adulthood onset TLE (peak of occurrence at age 27 years) (Janszky et.al, 2004). Childhood and teenage-onset TLE differ from a clinical aspect as well (et.al, 2004; Villeneuve and colleagues 2005). The present study further supports the claim that different TLE subtypes can be differentiated based on age at onset.

Lateralisation of vocalisation is not exclusively characteristic of humans: in vertebrates vocalisation is usually linked to the left hemisphere (Walker, 1980; Bauer, 1993). In humans and apes, electrical stimulation can evoke vocalisation from four cortical regions. These are the Broca area, the SMA, the anterior cingulate gyrus and the mediofrontal cortex (Penfield and co-workers, 1952; Erickson and Woolsey, 1951; Kirzinger and co-workers, 1982). In frontal lobe epilepsy examinations, the occurrence of PIV was explained by the spreading of epileptic activity to the Broca area or the supplementary motor area (Janszky and colleagues, 2000).

In TLE we cannot explain the exact mechanism behind the production of PIV, as according to current knowledge there is no structure within the temporal lobe that could produce vocalisation. One possible explanation is that PIV results from the spreading of electrical activity from the temporal regions to the Broca area via the available functional connections (eg. fasciculus arcuatus). Bartolomei and colleagues (2002) studied the anatomical and electro-clinical connections of ictal muttering in seizures of three TLE patients. Using intracerebral electrodes they could show that muttering during an epileptic episode may be related to the traveling of seizure activity from the upper temporal to the lower frontal gyrus. The present study did not find a correlation between PIV and perictal aphasia or PIV and mesial versus lateral TLE which contradicts the theory claiming that PIV results from the seizure propagating towards the temporolateral region or the lower frontal gyrus. It is also possible that in the background of PIV there is the spreading of epileptic activity starting out from the temporal focus into extratemporal limbic structures, for example the anterior cingulate cortex. This region is often activated during TLE episodes (Talairach and Bancaud, 1973) and stimulating it in apes produces vocalisations (Kirzinger and Jürgens, 1982).

2. Examination of preoperative surgical prognostic factors in amygdalar epilepsy

2.1. Methods

Patients enrolled into the study underwent a detailed preoperative epilepsy surgery examination. Inclusion criteria for pharmacoresistant TLE patients were the following: (1) pharmacoresistant TLE (2) prolonged video-EEG monitoring (3) preoperative skull MRI (4) presence of unilateral amygdalar lesion on the preoperative MRI without hippocampal abnormality (5) apical TLR between 2001 – 2007 with the hippocampus preserved (6) two-year-long postoperative follow-up focusing on seizure outcome.

MR images were reanalysed according to the following:

(1) presence of amygdalar lesion (2) absence of hippocampal abnormality (3) categorisation of amygdalar lesions based on the MRI.

The patients' interictal EEG recordings were examined on the basis of hourly two-minute recordings made during prolonged video-EEG monitoring. Based on these, we determined the incidence of IEP. Based on an earlier study (Kendl and colleagues., 2008), we called **IEP frequency high** if more than 60 IEP/hour was detected and **low** if it was less than 60 IEP/hour. IEP dispersion was also investigated. In 15 patients, sphenoidal electrodes were also used. The following clinical data were studied as potential preoperative predictors:

(1) age at time of surgery (2) sex (3) duration of the condition (4) age at onset of epilepsy (5) generalised tonic-clonic seizures (GTCS) (6) seizure frequency (7) family history of epilepsy (8) unilateral IEP (9) bilateral IEP (10) epilepsy risk factors in the medical history (11) absolute IEP frequency (12) type of amygdalar lesion based on preoperative MRI (13) extension of the amygdalar lesion on the preoperative MRI.

Apical TLR was performed in all the enrolled patients with the preservation of the hippocampus during surgery, the anterior part of the parahippocampal gyrus, the uncus, the temporal pole and the amygdala are removed. Our study intended to search for preoperative factors that could determine the prognosis of a two-year seizure outcome. Neuropsychological and psychiatric outcomes were not in the focus of the present study.

2.2.Results

42 patients met the inclusion criteria (18 females, 24 males), mean age was a 31.4+11 years, age at onset of epilepsy was between 1 and 56 years, disease duration ranged between 1 and 26 years. While PMS occurred in all patients, 32 had GTCS as well. Regarding epilepsy risk factors: 6 patients had epilepsy among first-degree relatives, four patients had had perinatal asphyxia, one meningo-encephalitis, and another three had had severe cranial trauma before the onset of epilepsy.

As regards electrophysiological data, only 4 out of the 42 patients had bilateral IEPs, the rest of the patients had unilateral IEPs above the operated temporal lobe. Analysing the interictal EEG recordings 9 patients showed high (> 60 IEP/hour), 33 patients low spike frequency (<60 IEP/hour).

Based on their appearance on preoperative MR images, amygdalar lesions were diagnosed as neoplasms in 19, as cavernomas in 5 and as dysgenesis in 4 cases by the neuroradiologist, in the remaining 14 cases the MRI lesions could not be categorised. aTLR was performed in all cases, in 20 cases on the right and in 22 cases on the left side. 71% of the 42 patients were seizure-free during the two-year follow-up. Histological examinations revealed neoplasms in 18 (9 gangliomas, 7 DNETs, 2 astrocytomas), cortical dysgenesis in 9 (3 polymicrogyrias, 6 focal cortical dysplasias), cavernoma in 3 cases, 1 patient had postencephalitis gliosis, in 6 cases non-specific gliosis was found and in 5 cases no histological changes could be found. In cases where the aetiology could not be categorised according to the MR images, one was diagnosed as DNET, two proved to be dysgeneses, 6 non-specific glioses and in the case of 5 patients there were no histological pathologies detected.

The prognostic significance of preoperatively defined variables upon seizure outcome was analysed using a multivariate, logistic regression method. As a result the following variables proved to be independent predictive factors with respect to successful surgery:

- (1) **low IEP frequency** ($p=0.013$, the odds ratio [OR] for seizure-free status OR= 25, 95% CI: 1.92-250)
- (2) **aetiology of a tumour** ($p = 0.027$, OR=14.2, 95% CI:1.35-142),
- (3) **negative family history** ($p=0.027$, OR=22.9, 95% CI:1.43-369)

In the low IEP frequency group, 79% while in the high IEP frequency group, 44% of the patients became seizure-free after surgery. The difference in IEP frequency between the seizure-free group and the group that continued to have seizures is significant even if we consider IEP a continuous variable. Among patients whose lesions were diagnosed as

neoplasms based on the MRI, 86% were seizure-free as opposed to those having lesions of other aetiologies where only 60% became seizure-free. In the case of positive family history 50%, in the absence of it 75% was the ratio of a seizure-free status. The use of sphenoidal electrodes, however, might have influenced the examination of IEP frequencies. On the other hand, the use of sphenoidal electrodes did not affect the correlation between the IEP frequency and two-year seizure outcome. Out of 15 patients 13 (87%) belonged to the low IEP frequency group, out of the remaining 27 patients (where we did not use sphenoidal electrodes) 20 (74%) also belonged to the low IEP frequency group: the difference was not statistically significant ($p = 0.45$, Fisher exact test). Out of those 15 patients, in the cases of whom sphenoidal electrodes were used, 11 were seizure-free two years after surgery (73%). Out of the other 27 patients, in whose cases no sphenoidal electrodes were used, 19 were seizure-free at the check-up examination after two years. (70%, $p = 1.0$, Fisher exact test).

2.3. Summary and interpretation of results

Our study intended to determine the prognostic factors of amygdalar epilepsy surgeries with the inclusion of 42 pharmacoresistant TLE patients with amygdalar lesions who had previous undergone surgery. As regards successful surgical outcome:

- (1) **high IEP frequency** and **positive family history** proved to be negative predictors for epilepsy,
- (2) while **aetiology of a tumour proved to be a positive** predictor.

Kendl and colleagues came to similar conclusions examining mTLE-HS: absolute spike frequency – irrespective of the locations or dispersion of spikes with respect to the surgical area - proved a potent predictor (Kendl et al., 2008). A limitation of this study however, was that it failed to consider several prognostic factors described in earlier studies (duration of condition, presence of GTCS). Thus it remained unclear whether IEP frequency was an independent prognostic factor for mTLE-HS surgeries. Another study also investigating TLE patients, found a significant correlation among higher IEP, longer duration of the condition and average seizure frequency. (Janszky and colleagues, 2005). Taking all this into consideration, based on our investigations, **the correlation between high IEP and a less favourable seizure outcome is not determined by seizure frequency or the disease duration.** Our investigation not only supports but further extends the results of Kendl and co-workers, from a patient population with HS-TLE to amygdalar epilepsy. In the background of the above correlation, it may also be supposed that during the scalp-EEG, IEPs originating

from the mesial temporal areas cannot be detected, only those segments which propagate towards the lateral neocortex. (Clemens and colleagues., 2003) Thus a higher IEP may also be indicative of a more expansive irritative zone which is only partially removed during resective surgery. A more extensive spreading of seizure is also a negative predictor of the outcome of TLE surgeries. (Schulz et al., 2000; Janszky et al., 2006). Besides high IEP frequency, positive family history also proved to be a negative predictor. In the background we may suppose, that due to a congenital predisposition, these patients generally possess a lower seizure threshold, consequently, they may have seizures originating from other regions of the brain, not directly from regions near the observable epileptogenic zone, which are not removed during surgery. The presence of a tumor on the preoperative MRI indicating a better postoperative seizure outcome. This correlation has been shown by several previous studies in mesial and neocortical TLE and also in connection with extratemporal resective surgeries (Janszky et al., 2006; Clusmann et al., 2002, Tonini et al., 2004). In our study, the suspected diagnosis of neoplasm based on the MRI was subsequently verified in all patients, by histological examinations. A tumour, usually, is a well-defined, localised lesion therefore, its complete resection – extended if required – is easier, (the epileptogenic lesion, and the EZ as well), and can most probably be resected in its entirety, which obviously means a better post-operative seizure outcome.

3. The use of R2* relaxometry in determining the epileptogenic zone during the surgical examination of temporal lobe epilepsy

The determination of the epileptogenic zone is a complex procedure requiring several different methods. The rapid and massive developments of the MRI era have provided a growing number of sequences, the clinical applicability of which in different neurological disorders have been studied intensely. R2* relaxometry is a quantitative MR technique; regarding its fundamental principles, the local increase of the inhomogeneity of the magnetic field leads to an increase of R2* relaxivity. The inhomogeneity of the magnetic field is increased by, among others, the presence or increased deposition of paramagnetic substances, such as iron. According to outcomes of earlier indirect followed by direct validation studies, the average R2* value correlates well with the iron content of the brain tissue. (Peran et al., 2009; Langkammer et al., 2010). Langkammer and his colleagues, in a post-mortem study, found a strong linear correlation between R2* relaxation and iron content in subcortical nuclei (Langkammer et al., 2010). Several earlier studies have shown the applicability of R2* relaxometry both to the healthy population (Aquino et al., 2009), and to neurological disorders causing a provenly increased iron deposition in the central nervous system (Novellino et al., 2013; Khalilet al., 2009; Khalil et al., 2011; Ulla et al., 2013; Langkammer et al., 2013). The presence of iron in the brain is physiological, it is mobilised (transferrin, H-ferritin) and stored (L-ferritin) mostly via binding to proteins. It has an essential role in physiological myelinisation, basic biochemical processes (RNA, DNA, protein synthesis), it is a co-factor of several enzymes (eg.: ATP production, cytochrome system, breathing chain, enzymes of neurotransmitter synthesis) (Hentze et al., 2010; Wang et al., 2011; Georgieff, 2008). Through the Fenton reaction, its inadequate sequestration and release results in the production of reactive free radicals and via induced lipid peroxydation it may lead to the destruction of cells (Singh et al., 2014). The roles of reactive free radicle production and induced lipid peroxydation in the development of epileptic seizures has been suggested by many earlier studies (Adibhatla and Hatcher, 2010), and is further supported by a study in which FeCl₂/ FeCl₃ were injected into areas of the neocortex and hippocampus in one of the most commonly used epilepsy models in rats (Mishra et al, 2010). The upregulation of ferritin was shown in a TLE rat model (status epilepticus enduced by electric stimulation), which gave a characteristic spatial dispersion and changes with time, in the mesiotemporal structures

(hippocampus, parahippocampal gyrus). In the acute phase in the hippocampus then in the chronic phase in the progressive group where following a period of latency recurrent seizure episodes occurred in the parahippocampal cortex (Gorter et al., 2005). Following contusions and intracranial bleedings of various severity related to penetrating and non-penetrating skull traumas, there is a 20-50% chance for the development of post-trauma epilepsy. In the background of the generation of late, recurrent seizures, the pathophysiological roles of post-traumatic regional iron deposition and a consequent free radicle production are supposed. (Payan et al., 1970; Willmore, 1990; Agrawalet al., 2006). Free radicle production induced by iron causes the lipid peroxydation of neuronal membranes, thus may generate epileptogenic foci. In status epilepticus, free iron accumulating in mitochondria inhibits physiological cellular functioning, thereby contributing to the injuries to and destruction of hippocampal neurons. This is further supported by the fact that in animal models the binding of mitochondrial free iron precedes the mitochondrial dysfunction and destruction of neurons caused by an epileptic seizure (Liang et al., 2008).

In the present study, we examined the dispersion of iron in the hippocampus, the amygdala, the thalamus and the pallidum in patients with TLE associated with eHS with quantitative $R2^*$ relaxometry.

3.1.Methods

Eight patients (6 females) with unilateral mTLE-HS (5 left, 3 right-sided HS) were enrolled into the study. Mean age was 40.50 ± 18.00 years, mean age at onset of epilepsy was 19.75 ± 23.16 years, disease duration was 20.75 ± 22.22 years, the average monthly frequency of PMS in the year prior to the study was 6 ± 6.43 years. Participating patients were patients treated at the Department of Neurology, University of Pécs. Exclusion criteria included alcohol and drug abuse, psychiatric disorders, brain trauma in the medical history, cerebrovascular diseases and inadequate MR image.

In our investigation a 3T Magnetom TIM Trio whole body MRI machine with a 12-channel head coil was used (Siemens AG, Erlangen, Germany). The conventional protocol contained a T2-weighted 2D turbo spin-echo sequence. For $R2^*$ images a multi-echo 3D FLASH sequence was used with 12 echos. The calculation of the $R2^*$ map was done with the help of Matlab (MathWorks, Natick, MA). To this we adjusted an equation describing monoexponential decrease in signals (i.e. $STE = S_0 \cdot e^{-TE \cdot R2^*}$) onto each voxel with the non-linear smallest squares method. The calculated $R2^*$ maps were registered onto high definition three-dimensional, T1 weighted MPRAGE images (6 degrees of freedom) with the help of the

FLIRT contained in the FSL programme package. For the calculation of regional $R2^*$ values, the volumes of examined structures (hippocampus, amygdala, thalamus and pallidum) were retrieved and segmented with the help of FIRST contained in the FSL programme package on T1 weighted MPRAGE images. Segmented masks were eroded with the help of a $3 \times 3 \times 1$ 2D kernel in order to reduce the number of errors arising from partial volume effect and registration ($R2^*$ - MPRAGE).

3.2.Results

In the TLE-HS patient group we compared $R2^*$ values of the affected side (ipsilateral) hippocampus, amygdala, thalamus és pallidum with $R2^*$ values of the same structures of the unaffected side (contralateral). Out of the four structures, the hippocampus in the affected side showed a significantly decreased $R2^*$ value (mean value of the affected side: $15.04 \pm 1.48 \text{ sec}^{-1}$, mean value of the contralateral side: $15.98 \pm 1.9 \text{ sec}^{-1}$). The difference was significant ($p=0.036$, Wilcoxon test). Since it is known, that hippocampal sclerosis results in selective destruction of neurons and gliosis, the noticed differences may have been caused by the difference in volume between the two hippocampi. No correlation was found upon examining the potential correlations between $R2^*$ values and volumes of the ipsi- and contralateral hippocampi.

3.3.Summary and interpretaion of results

Our preliminary results revealed, that in mTLE-HS, $R2^*$ relaxometry on the same side of the HS (ipsilaterally) showed a **significantly lower** $R2^*$ value. This result points out the adequacy and future applicability of the method for the localisation of EZ in non-lesional cases. The difference suggesting lower iron content is surprising, since brain damage usually presupposes higher iron content together with an epileptic functional disturbance. To date, there has been one study on this topic in TLE, but that study used SWI sequence (Zhang et al, 2014). The SWI sequence is less quantifiable than $R2^*$ relaxometry. The study revealed decreased iron content in the nucleus ruber, the substantia nigra and the basal ganglia (globus pallidum, putamen), but increased iron content in the cortex. The negative correlation found between the cortical and subcortical iron content raised the idea of the possible role of a redistribution of intracerebral iron in the pathogenesis of epilepsy. (Zhang et al., 2014). Although, the above study used a different method and did not examine the vital mesiotemporal structures in TLE (hippocampus and amygdala), our results correspond to the hypothesis which holds that in epilepsy, iron content decreases in subcortical regions. At present, there is no straightforward explanation for the detected lower $R2^*$ values in the cases

of sclerotic hippocampi. As hippocampal sclerosis is a special, unique entity, with its pathomechanism still, to a certain extent, being unclear (Malmgren and Thom, 2012), the pathophysiological role of iron in its development remains to be further investigated, as opposed to neurodegenerative disorders and post-traumatic/post-stroke epilepsy, where the prooxidative/cytotoxic effect of accumulating iron has been shown. (Stankiewicz et al., 2007; Agrawalet et al., 2006). As all examination methods, R2* relaxometry also has its limitations, therefore, it is important to consider that measured R2* values change according to effects locally increasing the inhomogeneity of the magnetic field, that is, macroscopic susceptibility artefacts (vascular, microstructural differences, meeting points of neighbouring surfaces) or other metals with para or diamagnetic features and the presence of minerals (calcium, copper, manganese).

Summary of novel results

1. The present study was the first to verify the lateralisation value of ictal vocalisation in TLE: it more commonly accompanies left-sided (dominant) TLE.
2. Our study found, that in the case of amygdalar epilepsy, during the examination of preoperative prognostic factors indicating surgical outcome, high interictal epileptiform potential frequency and positive family history proved to be negative predictors, while aetiology of a tumour on the preoperative MRI proved to be a positive predictor.
3. We were the first to suggest that in TLE associated with hippocampal sclerosis, according to the epileptogenic zone, lower R2* values were detected ipsilaterally in the hippocampi, this decrease, however, did not show a correlation with the decrease in the volume of the affected hippocampi.

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Publications

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Impact factor: 4.052

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Impact factor: 2.302

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SCIENTOMETRIC DATA

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