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R^{2*} Relaxometry in Sclerotic Hippocampi of Patients with Temporal Lobe Epilepsy

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Abstract

Pharmacoresistance to antiepileptic therapy is a frequently observed phenomenon in mesial temporal lobe epilepsy with hippocampal sclerosis (HS-TLE). Neurosurgical intervention can be an alternative treatment in drug-resistant HS-TLE patients. Several studies have already proven that in unilateral MRI abnormality, which is most frequently hippocampal sclerosis, predicts a more favorable seizure outcome.

MRI characteristics of hippocampal sclerosis are well discribed in the literature of neuroimaging. In most cases, hippocampal sclerosis can be detected by atrophy and T2 signal abnormalities, however, there is a number of subtle primary findings and negative cases as well. The diagnosis of TLE can be supported by the measurement of quantitative secondary MRI signs on the pathological side. R2* relaxometry is a quantitative approach in magnetic resonance imaging. The technique is based on the local increase of the inhomogenity of the magnetic field that results in an increase of R2* relaxivity. There has been one hitherto published study on this topic in literature, which was based on SWI imaging regardless to the specificities of the hippocampus. The aim of this study is to investigate the utilization of R2* relaxometry in patients diagnosed with HS-TLE.

Methods

Thirteen patients (10 females, mean age: 41.5 ± 15.4 years, range: 19–63 years) with temporal lobe epilepsy associated with unilateral hippocampal sclerosis (4 right-sided, 9 left-sided) were enrolled in the study compared with thirteen age- and gender matched healthy control subjects (mean age: 41.9 ± 15.3 years, range: 19–66 years). Beside the MRI with epilepsy-specific protocol, MRI with research protocol was also obtained for all patients between January 2013 and June 2015 at least 48 hours following the last seizure. For R2* mapping a multi-echo 3D FLASH sequence was used with 12 echoes. The calculation of the R2* map was done with the help of Matlab (MathWorks, Natick, MA). To obtain regional R2* relaxation rate of the hippocampus, automatic hippocampal segmentations were performed on T1-weighted MPRAGE images.

Results

The R2* values were found significantly decreased in the ipsilateral, sclerotic hippocampi of patients with HS-TLE compared to the corresponding side of control subjects ($p<0.001$) or the contralateral side of the same subject ($p=0.002$). Comparison of the contralateral, non-sclerotic hippocampi of HS-TLE patients and the corresponding site of the controls did not show significant difference. Focusing on the control group, there was no significant inequality in R2* values between the hippocampi of the two sides (corresponding ipsi- and contralateral sides of patients). Examination of the potential connections between the volumes and R2* values of the ipsi- and contralateral hippocampi, no significant correlations were found neither in the HS-TLE, nor in the control group.

Conclusion

R2* relaxometry might be an additional method to assess the lateralization of hippocampal pathologies in patients with HS-TLE.

Keywords: epilepsy, R2* relaxometry, hippocampal sclerosis.

Introduction

Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS) is the most prevalent focal epilepsy syndrome in adults [1] [2] [3].

Patients with MTLE-HS frequently develop pharmacoresistance to antiepileptic treatment. In case of drug-refractory TLE, surgical removal of the epileptogenic lesion provides a therapy option with high potential for seizure control. Several studies proved that in patients with unilateral lesion on the MRI – most frequently hippocampal sclerosis –better postoperative seizure outcome is expected. [4] [5] [6] [7] [8] [9] [10] [11]. Meta-analysis of Téllez-Zenteno et al. demonstrated that the chance for being seizure-free after surgery are two to three times higher in the presence of MRI-detectable lesion [12]. The principal MRI signs of hippocampal sclerosis – hippocampal atrophy and hyperintense T2-weighted and/or fluid-attenuated inversion recovery (FLAIR) signal – are well documented in neuroimaging studies [13] [14] [15]. Hippocampal sclerosis can be detected based on atrophy and abnormal T2 signal in the majority of the cases, but there are a lot of cases with MRI-negative or subtle primary findings.

Quantitative and qualitative secondary MRI signs (such as T2 values, NAA values, hippocampal volume, temporal horn dilatation, collateral white matter atrophy, loss of the normal internal architecture of the hippocampus, smaller fornix or mamillary body, loss of digitation of the hippocampal head) via the lateralization of temporal lobe or hippocampal abnormalities may support the diagnosis of temporal lobe epilepsy beforehand based on electroclinical data b[13-23]. T2 relaxometry is able to lateralize the epileptogenic focus in sclerotic hippocampus and also in MRI-negative TLE patients. The sclerotic hippocampus is typically accompanied by an increased T2 relaxation time[24,25]. R2* (1/T2*) relaxometry is another promising quantitative MR technique and seems to be useful in numerous central nervous system diseases. A significant number of earlier studies have shown that of R2* relaxometry can be applied both in healthy population [26,27], and in neurological disorders with iron deposition in the central nervous system [28-32].

Regarding its basic principles, the increase of the magnetic field inhomogenity consequently leads to an increased R2* relaxivity. The presence or increased amount of para- or diamagnetic substances, such as iron, copper, zinc, manganase, calcium increases the inhomogenity of the magnetic field. According to outcomes of earlier studies followed by direct validation, the mean R2* value is strongly associated with the iron content of the brain tissue [33,34]. A postmortem study by Langkammer et al., found that in subcortical nuclei, a strong linear correlation between R2* relaxation rate and iron content can be found [34].

So far, there has been only one study on this topic in temporal lobe epilepsy [35]. This study suggested reduced iron content in the nucleus ruber, the substantia nigra and the basal ganglia (globus pallidum and putamen), however, iron content in the cortex measured by susceptibility-weighted imaging (SWI) was increased.

The negative correlation between the cortical and subcortical iron content raised the possibilty of a redistribution of intracerebral iron in the pathogenesis of epilepsy [35]. However, the above-mentioned study used an SWI based method and did not examine the hippocampus.

The aim of this study is to investigate the benefit of R2* relaxometry in patients with MTLE- HS in localizing or lateralizing epileptic foci. In addition, we would liketo add further information on altered metal homeostasis in sclerotic hippocampi via this method.

Methods

The experimental protocol was approved by the local ethical committee and performed in accordance with the ethical standards described in the Declaration of Helsinki (1964). Participants were informed about the process, and given an informed consent prior to the examination.

Subjects

Inclusion criteria for patients were the following:

- detailed presurgical assessment or under the care of an outpatient institution;
- head magnetic resonance imaging (MRI) with epilepsy-specific protocol;
- unilateral hippocampal sclerosis detected by MRI;

13 patients (10 females; mean age: 41.5 ± 15.4; range: 19–63 years) with TLE accompanied by unilateral hippocampal sclerosis were engaged in the study (4 right-sided, 9 left-sided). All subjects in the study presented initially to the tertiary epilepsy center and underwent 32- to 64-channel surface noninvasive electroencephalogram (EEG) monitoring, placing the electrodes according to the 10–10 system. Individual changes in the number of electrodes and their placement corresponding to the suspected epileptogenic region and localization were applied, however, FP1, F3, C3, P3, O1, F7, FT7, T7, TP7, P7, FT9, TP9, homologous right-sided electrodes, PZ, CZ, FZ were used everytime.

We carried out an adult presurgical evaluation protocol in nine patients including the following: (1.) continuous video-EEG monitoring, (2.) neuropsychological testing, and (3.) high-resolution head MRI with epilepsy-specific protocol. The remaining four patients were examined with long-term EEG, and they also had high-resolution head MRI with epilepsy-specific protocol. Clinical MR images were evaluated by a specialist in neuroradiology (P. Ba.). Patients wit, intracranial neoplasms, neurodegenerative disorders, major cognitive deficits and

patients with brain surgery in previous history were excluded from the study. The following clinical data were collected from every patient with TLE-HS previous to the MRI scan: age at study, sex, seizure frequency, age at epilepsy onset, epilepsy duration, level of education, history of febrile seizure, occurrence of generalized tonic–clonic seizure within the last 5 years, presence of aura, current antiepileptic drugs, head trauma prior to epilepsy-onset, history of encephalitis/meningitis, and possible perinatal complication were based on the heteroanamnesis. Seizure frequency was calculated from the seizure diary completed by the patient and defined as the mean of the number of monthly complex partial seizures during at least the last 12 months prior to enrollment. All patients were taking regular antiepileptic medication all along the study. Clinical and demographic data of patients with TLE-HS are summarized in Table 1.

Table 1. Electroclinical and demographic data of TLE-HS group (initial precipitating injury(IPI): febrile seizure/CNS infection, perinatal complication, head trauma; GTCS: generalised tonic-clonic seizure; HS: hippocampal sclerosis; AED: antiepileptic drugs; VPA: valproic acid, LTG:lamotrigin, LEV: levetiracetam, CLZ:clonazepam, CLB: clobazam, CBZ: carbamazepin, OXCBZ: oxcarbazepin, LCM:lacosamid, GBP:gabapentin; ED: epileptic discharge; VEEG: video-EEG monitoring).

	sex	Age at study (year)	Age at epilepsy onset (year)	Epilepsy duration (year)	GTCS during the last 5 years	CPS/ month	IPI	aura	St. epilepticus	MRI	EEG	AED
M.A.	female	20	17	3	-	18	+	epigastric	-	left HS	VEEG: not detected ED or seizure	VPA,LTG,CLB
T.B.	male	19	2	16	-	3	+	-	-	left HS	VEEG : left temporal ED; left temporal seizure-onset pattern	VPA,LCM
A.B.	female	48	4	44	-	6	+	non-specific	-	left HS	VEEG: right/left temporal ED; left temporal seizure-onset pattern	CBZ,LEV,CLB
Cs.K.	female	35	6	28	-	13	+	epigastric	-	left HS	VEEG: right/left temporal ED; left temporal seizure-onset pattern	OXCBZ, CLZ
Gy.D.	female	63	57	6	+	6	-	-	-	left HS	VEEG: right/left temporal ED left temporal seizure-onset pattern	GBP,VPA,CLB
I.L.	female	61	1	60	-	0	+	-	-	right HS	long term EEG: right	VPA,LTG

											temporal ED	
V.C.	female	22	16	6	-	2	-	-	-	right HS	VEEG: right/left temporal ED; right temporal seizure-onset pattern	LEV,LCM,CLB
I.B.	male	51	26	27	-	0	-	epigastric	-	left HS	VEEG: right temporal ED, not detected seizure	OXCBZ
T.Sz.	female	39	31	8	-	0	-	Dejavu/ epigastric	-	left HS	long term EEG :right temporal ED	LEV,LTG
T.L.	female	35	10	25	-	2	-	epigastric	-	left HS	VEEG: left temporal ED, not detected seizure	LEV,LTG
L.B.	male	36	35	1	+	1	-	-	-	left HS	long term EEG:left temporal ED	VPA
A.H.	female	53	16	37	+	2	+	non-specific	-	right HS	VEEG: right frontotemporal ED, right temporal seizure-onset pattern	LTG,VPA
F.S.	female	58	47	11	-	2	-	-	-	right	long term EEG: right temporal ED	CBZ

Thirteen age- and gender-matched healthy control subjects (10 females; mean age: 41.9 ± 15.3, range: 19–66 years) were also examined. Volunteers from the control group were excluded if they had alcohol or drug abuse, psychiatric illness, traumatic brain injury, or history of significant medical or neurological conditions that would be associated with remarkable changes in the brain.

Magnetic resonance imaging

All measurements were performed on a 3T Siemens MAGNETOM Trio MRI scanner with a 12-channel head coil. In all patients, at least two MRI examinations were performed:

- (I) An MRI with epilepsy-specific protocol: it is part of our standard clinical practice and screening for hippocampal sclerosis was performed as it was an inclusion criterion for this study. The epilepsy-specific protocol also contained the 2D FLAIR imaging sequence with fat suppression and T1-weighted high-resolution images (voxel size: 0.98 × 0.98 × 0.98 mm3) and DWI (diffusion weighted imaging) sequence besides the routine measurements (axial, coronal T2- weighted). itt csak szórendet cseréltem
- (II) An MRI with research protocol was also carried out for all patients between January 2013 and June 2015 at least 48 h after the last seizure. The general protocol contained a T2-weighted 2D turbo spin-echo sequence.

R2* mapping was based on a multi-echo 3D FLASH sequence with 12 equally spaced echoes (TR/TE1=47/3.58 ms; inter-echo spacing=3.53 ms; Flip Angle=16°; 104 axial slices; slice thickness=1mm; FOV=208x256 mm2; matrix size=208x256; receiver bandwidth=300Hz/pixel). For tissue segmentation and registration, a T1-weighted 3D magnetization-prepared rapid gradient echo (MPRAGE) sequence was utilized using the following parameters: TR/TI/TE=2530/1100/3.37 ms; Flip Angle=7°; 176 sagittal slices; slice thickness=1mm; FOV=256x256 mm2; matrix size=256x256; receiver bandwidth=200 Hz/pixel.

Hippocampus were segmented automatically on T1-weighted MPRAGE images using FIRST. The quality of segmentations was visually checked for all participants.

R2* maps were calculated by voxel-wise nonlinear least-squares fitting of the mono-exponential signal decay over echo time (i.e. STE=S0·e-TE·R2*, where STE is the measured signal intensity at time TE and S0·is a constant) using Matlab (MathWorks, Natick, MA). In order to derive R2* values of the hippocampus, R2* map of each subject was linearly registered to that subject's MPRAGE image (6 degrees-of-freedom linear fit) using FLIRT. Finally, the inverse of the spatial transformation from R2* map to MPRAGE space was applied to align the segmented brain masks to R2* map space, where R2* values were obtained.

The resulting masks were eroded by using a 2D kernel of 3x3x1 voxels to avoid partial volume effects and to minimize possible impacts of misregistration between R2* maps and MPRAGE images. R2* values were calculated for the eroded structure and obtained separately for both the left and the right hippocampus.

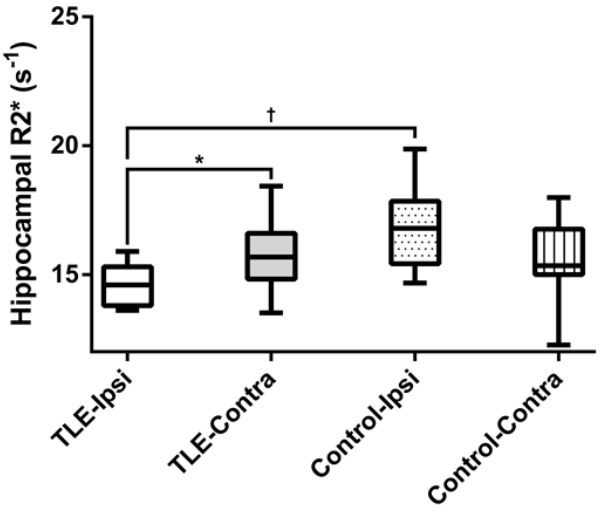
Statistical evaluation

SPSS® statistical software version 21.0 (IBM Corp., Armonk, NY) was used for data analysis. Differences of R2* values of hippocampi between TLE-HS patients and age/sex matched control subjects were calculated by Wilcoxon test. Among TLE-HS patients differences of R2*values of sclerotic and non-sclerotic hippocampi were estimated by Wilcoxon tests (2-tailed). Among control group differences of R2*values of right and left hippocampi were estimated by Wilcoxon test (2-tailed). The correlation of clinical data with R2*values was measured by Spearman's correlation. The correlations between the volumes and R2* values of the ipsi- and contralateral hippocampi were examined by Spearman's correlation. Results were considered significant at $p \leq 0.05$ for all statistical tests.

Results

The R2* values were significantly reduced in the ipsilateral hippocampi of temporal lobe epilepsy patients with sclerotic hippocampi compared to the analogous side of control subjects ($p<0.001$) or compared to the contralateral side of the same patients ($p=0.002$) (figure 1.). No significant differences were detected in R2* values between the contralateral hippocampi of TLE-HS patients and the corresponding side of the controls (Wilcoxon, 2-tailed, $p=0.810$). Examining only the control group, no significant difference can be found in R2* values between the two sides of hippocampi (Wilcoxon, 2-tailed, $p=0.102$). We found no correlation between the volumes and R2* values of the ipsi- and contralateral hippocampi in either group. Positive correlation between age and R2* values in sclerotic hippocampi was found examining the connection of R2* values with parametric clinical data (age, seizure frequency, age at epilepsy-onset, disease duration).

Figure 1: Boxplot illustrating the significantly decreased R2* relaxation rate in the ipsilateral hippocampi of TLE-HS patients compared to the corresponding side of controls († P<0.001, 2-tailed Mann-Whitney U Test) or compared to the contralateral side of the same patients (* P=0.001, 2-tailed Wilcoxon signed-rank test). Whiskers are set at minimum and maximum, the horizontal line marks the median, whereas box indicates the interquartile range (25-75%). Ipsi/Contra=Ipsilateral/ Contralateral side of the patients and the corresponding side of the matched controls. In case of the contralateral side of controls one outlier subject was removed, thus the boxplot is based on 12 subjects.



Conclusions

This is the first study, which investigates the alteration of R2* values in sclerotic hippocampi of TLE-HS. The major findings are as follows:

- Sclerotic hippocampi associated with decreased R2* values
- We found no correlation examining the potential connections between R2* values and volumes of the hippocampi in bot sides, both in control and TLE-HS group.
- Positive correlation between age and R2* values in sclerotic hippocampi can be detected.

Our findings, decreased R2* values in sclerotic hippocampi, are in accordance with the results of T2 relaxomtery studies [25] [24] [36]. The underlying pathology of these findings is unknown. Previous studies have reported that hippocampal T2 relaxation time might be associated with injury of CA1 region and hilus [37], neuronal density in CA1/CA3 hippocampus subfield [38] and astrogliosis in the dentate gyrus [39]. These studies examined the correlation of the T2 relaxation time with the classic histopathological signs of hippocampal sclerosis [40]

and did not investigate other detectable pathological changes in sclerotic hippocampi, as for example the alteration of antioxidative system [41], mitochondrial dysfunction [42], mossy fibre sprouting [43], atrophic microvasculature [44], downregulation of glutamine synthetase [45]. However the above mentioned changes, may result in alteration of metal content [46] in sclerotic hippocampi. Certain metal ions can act as enzyme cofactor or cotransmitter in synaptic transmission. The increase or decrease of para - or diamagnetic elements, such as iron, copper, zinc, manganase, calcium lead to increased or decreased local inhomogenity of the magnetic field. Based on this phenomena, R2*relaxometry can be a supplementary option to delineate hippocampal abnormalities in TLE patients. It has been proven that the sclerotic hippocampi of TLE patients are exposed to excessive oxidative stress and shows mitochondrial dysfunction. Mitochondrial dysfunction is not only a result of seizures but may also be a triggering factor of chronic epilepsy [47] [48] [49] [50]. Mitochondrial oxidative phosphorylation is the most important producer of ATP in cells and mitochondria take part in cellular Ca(2+) balance as well. Superoxide (O2-) is mostly produced by complex I. in mitochondria. Decreased activity of mitochondrial complex I. has been described in epileptic sclerotic hippocampi in TLE patients, which can lead to increased superoxide production [42]. Superoxide is dismutated to H2O2 via MnSOD (manganese superoxide dismutase) in mithochondria and via CuZnSOD (copper-zinc superoxide dismutase) in cytosol. Superoxide-derivative (H2O2) is broken down to water by upregulated CAT (catalase) glutathion peroxidase or peroxiredoxin system. Mitochondrial dysfunction is known to be a triggering factor of neuronal cell death, which is a characteristic feature of sclerotic hippocampi. Parallel with selective neuronal loss and astrogliosis, it has been shown that there are an increased activity/level of the above mentioned oxidative enzymes and an altered subfield-specific distribution in the epileptic sclerotic hippocampi of TLE [41]. As cofactors copper and manganase, are required for the above mentioned enzymes to be catalytically active in mitochondria, cytosol in both neurons and asrocytes. The aberrant mossy fibre sprouting is another feature of hippocampal tissues from TLE patients, defined as the growth of dentate granule cell axons into their individual dendritic field in the inner molecular layer, providing a repetitive excitatory pathway. Along with releasing glutamate, these recurrent collaterals also release zinc. Zn is present in the axon terminals of granule cells (mossy fibers). Zn can be visualized by Timm's staining [51] [52]. During normal synaptic activity as well as during stimulation, Zn is relased from the axon terminals [53] [54] [55]. Zn is a cotransmitter and block NMDA receptors on CA3 pyramidal cells during normal synaptic transmission [43], and can also modulate different neurotransmitter receptors [56].

Timm's staining reveals that the overwhelming majority hippocampal Zn content is localized to a relatively small area of hippocampal formation, in the hilus of the dentate gyrus and in the str. lucidum of CA3 region [57] [58].

In animal models of epilepsy, the decrease of the intensity of Timm staining was found due to depletion of Zn from axon terminals [57] [59] [60]. In most of the cases, a difference was found between the ispi and contralateral hippocampi, and the decrease in staining intensity was more pronounced in the ipsilateral side [57]. Due to relase of Zn from synaptic terminals, concentration of extracellular Zn will be increased, and Zn can be taken up by neurons [61]. In animal models of epilepsy, change in the pattern of Timm staining (due to sprouting) was found [62] [63].

In TLE patients, due to the sprouting of mossy fibers, the distribution of Zn containing axon terminals is changed, because Zn containing axon teminals are present, in addition to tha hilus and the str lucidum of CA3, in the molecular layer of the dentate gyrus [64].

In non-human primate – similar changes are seen [65]. In the epileptic dentate gyrus during recurrent seizures high amount of zinc can be released form mossy fiber terminals resulting of high extracellular concentrations which can lead to excitotoxic neuronal death and modulation of postsynaptic neighboring inhibitory (GABA) receptors [66]. Based on this we clearly see the change in distribution and decrease of Zn content in epilepsy that may result in a decrease inhomogenity of Zn distribution, therefore decrease of the magnitic field inhomogenity, that equals with decreased R2* value.

Sclerotic hippocampi of operated TLE patients showed lower managanase and copper levels compared with non-sclerotic control hippocampi using inductively coupled plasma optical emission spectrometry [67]. Manganase is a cofactor for multiple enzymes, like glutamine synthetase (GS) in astrocytes [68]. Glutamate released from synapses due to neuronal activity is normally taken up by astrocytes and converted to glutamine by glutamine synthetase [69]. GS is a metalloprotein, which requires metal ions -manganase – for catalysis. It has been proved that deficiency of GS is likely to lead to the accumulation of extracellular glutamate and seizure generation via binding of glutamate to neuronal glutamate receptors [45] [70]. Beyond these changes, the sclerotic hippocampi were depleted of glutathion peroxidase positive blood vessels and glutathion peroxidase rich sites were revealed in these tissue samples [41]. These sites are likely to represent a group of asrocytic bundles, which might compensate the excessive neuronal production of superoxide-derivative [41]. According to this, it has been well documented that sclerotic hippocampus of TLE-HS patients show atrophic microvasculature in spite of apparent increased blood vessel density [44] [71] compared to controls. Immunohistochemistry studies (collagen type-IV) revealed that an angiogenesis has occured but the surface of these vessels have a number of small, tubular-like protrusions based on the results of the light- and electromicroscopy studies. These altered vasculature have virtually absent or reduced lumen filled with reactive astrocytes [44] [71]. In adults more than half amount of total iron content is incorporated into haemoglobin mainly in red blood cells. Taken together, the atrophic microvasculature in sclerotic hippocampi might be accompanied by decreased heme iron content due to the reduced blood supply.

One distinctive charateristic of neuroinflammation is the activation and increased acquisition of extracellular iron and consecutive downregulation of iron-interacting proteins, causing the intracellular sequestration of iron [72]. Intracellular iron

accumulation is associated with neuronal degeneration that befalls most neurological diseases [73], and microglal secretion of inflammatory cytokines (TNF-alfa, IL-1) increasing iron uptake of neurons [74]. However, the mentioned inflammatory mediators have been shown to have a significant effect on iron transport and metabolism of microglia [72] [75] [76] [77].

We found positive correlation between R2* values in sclerotic hippocampi and the age of patients. In our study most of the patients (n=9) had left hippocampal sclerosis on the MRI scans. It has been known the hippoacmpal volume differences between the left and right side in the normal subjects (R > L) [78]. The exact cause is unknown, but it has been proved that the left hippocampal MR abnormalities are more pronounced in some neurological disease for example mild cognitive impairment [79] or after febrile convulsion [80] [81]. These findings support the hypothesis that the right and left hippoacmpus differ in their vulnerability to neurological insult.

In the present study we used R2* relaxometry to assess the hippocampi of temporal lobe epilepsy patient. This method is much more sensitive to changes in iron concentration than R2 relaxometry, and has similar sensitivity as the more complex quantitative susceptibility mapping (QSM) approach [34] [82]. It has to be noted that gradient echo phase image can also be used to assess magnetic susceptibility and the method was also applied in TLE [35]. However, filtered phase image has been systematically researched so far only in a small number studies [82]. In contrast, R2* mapping is a strong and well-established approach utilized in a number of studies [82]. It does not include complicated evaluation steps and the required multi-echo gradient echo sequence and fully automatic T2* map calculation option are readily available on most clinical scanners.

Altered R2*relaxometry of the sclerotic hippocampi might be multifactorial: it might beinfluenced by the loss of metal homeostasis as well. Regardless of the exact cause of decreased of hippocampal R2* values, it might help in localizing the epileptogenic zone in TLE. The so-called secondary MRI-signs are particularly important in those cases where conventional MRI scans do not show clearcut epileptogenic lesion - e.g. classical MRI signs of hippocampal sclerosis (atrophy, T2/FLAIR hyperintensity) - but the electroclinical data suggest unilateral mesial TLE. R2* relaxometry might add to the inventory of quantitative secondary MR signs, which could be used in localizing epileptic foci and planning surgery or invasive EEG monitoring.

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