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^{1}H-MRS profile in MRI positive- versus MRI negative patients with temporal lobe epilepsy

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Summary

Introduction: The objective of this study was to quantitate and compare ipsilateral total *N*-acetyl aspartate (tNAA), creatine (Cr), choline (Cho), myo-inositol (m-Ins) and glutamate plus glutamine (Glx) levels in the hippocampi of patients with temporal lobe epilepsy (TLE) with and without magnetic resonance imaging (MRI) evidence for mesial temporal sclerosis (MRI positive/negative).
Patients and methods: Twenty-three age matched healthy controls and 26 consecutive patients with unilateral TLE, based on intensive 24 h video-EEG, were investigated with proton magnetic resonance spectroscopy (^{1}H-MRS) (17 with unilateral hippocampal sclerosis (HS) in MRI—MRI positive; 9 MRI negative). For statistical analysis one-way analysis of variance (ANOVA) with post hoc multiple comparisons and Bonferroni correction was applied. The significance level was based on $p < 0.05$.
Results: The mean tNAA level ipsilateral to the seizure focus was significantly decreased in MRI negative, respectively MRI positive patients in comparison to healthy controls ($p < 0.001$). The lowest tNAA level was noticed in the MRI positive group ($p < 0.001$). Statistical analysis highlighted a clear "tNAA cut-off" (95% confidence interval) between MRI positive- and MRI negative patients and healthy controls. Mean level of Glx and m-Ins was not significantly elevated or reduced. However, in individual cases a significant elevation was noticed for Glx in MRI negative patients, respectively for m-Ins in MRI positive patients.

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Conclusion: MRI negative TLE patients have a different MRS profile than MRI positive patients (HS) with marginal but significant decrease of tNAA. Our results reveal a clear "tNAA cut-off" between the groups. The value of m-Ins and Glx in focus detection in TLE patients remains controversy.

Introduction

Hippocampal sclerosis (HS) is the most common finding in patients with temporal lobe epilepsy (TLE). It can be verified with high reliability (up to 90% sensitivity and 85% specificity) using magnetic resonance imaging (MRI) and is believed to reflect a combination of initial damage from an early injury and subsequent seizure-associated damage.[1–4] However, no pathological MRI findings in TLE patients are reported in up to 30%.[5,6] It remains controversy whether this is due to initial disease stages which do not display lesional findings in MRI because of subtle tissue alterations or based on different illness-entities affecting hippocampal structures.[7] In case of initial disease stage high field MRI of 3 T or above might be able to detect more subtle tissue pathology.

The search for metabolite alterations which are involved in the epileptogenic process is the topic of recent studies which try to enlighten the underlying pathology. Proton magnetic resonance spectroscopy (^{1}H-MRS), which is a non-invasive tool used in clinical settings, plays an increasing role in the detection of metabolite alterations in the mentioned patient group.[6,8–11] Measurements of total *N*-acetyl aspartate (tNAA) have proven to be reliable in lateralizing the affected hemisphere in patients with TLE. A decrease of tNAA is accepted as an objective marker for neuronal loss or dysfunction.[10,12–14] The excitatory amino acid neurotransmitters glutamate and glutamine have been consistently involved in the pathophysiology of TLE. ^{1}H-MRS studies reported that glutamate plus glutamine (Glx) levels are increased ipsilateral, respectively contralateral[15] to the seizure focus in MRI negative TLE patients.[11,14–16] However, a recent 3 T study found no significant differences in Glx concentrations in TLE patients in comparison to healthy controls.[17] Other ^{1}H-MRS studies of TLE have focused on myo-inositol (m-Ins) which has been implicated in intracellular signalling and in osmoregulation.[18] In mesial TLE reduced and elevated m-Ins concentrations have been described in the epileptogenic foci.[4,19]

The objective of this study was to investigate specific metabolic changes of tNAA, creatine (Cr), choline (Cho), m-Ins and Glx levels in the hippocampi of TLE patients with and without MRI evidence for mesial temporal sclerosis (MRI positive and MRI negative). Different metabolite alterations were attributed to the mentioned entities in order to specify and localize the primary epileptogenic regions. This information is important for understanding of underlying pathogenesis and prospectively therapeutic schedules.

Patients and methods

Subjects

Twenty-three control subjects (median age 34, 22—48 years) and 26 consecutive patients diagnosed with TLE (median age 35, range 19—62 years) were investigated with ^{1}H-MRS. Diagnosis of unilateral TLE was based on clinical history, seizure description and results of intensive video-EEG monitoring. All patients were very homogenous in clinical features and suffered from epilepsy with simple partial, complex partial and secondary tonic—clonic seizures. All patients were classified as unilateral by interictal/ictal EEG recordings. Nine TLE (median age 33, range 23—45 years) patients demonstrated no lesional findings in MRI (MRI negative) as determined by two independent and experienced neuroradiologists. Seventeen TLE patients (median age 36, range 19—62 years) showed ipsilateral lesional findings (MRI positive) to EEG. MRI imaging gave evidence for HS by hippocampal atrophy and signal increase in T2 weighted (T2w) images. Patients with HS in MRI were operated and showed HS in their specimen which was analyzed in our neuropathological institute.

EEG monitoring

The simultaneous registration of continuous video-EEG monitoring was performed using the Glonner system (Munich, Germany). Patient behaviour was recorded via a split-screen technique day and night over a period of 1—2 weeks. Technical details are: number of EEG/Polygraphic channels 64/128, sampling rate 200 Hz; storage of video-EEG data on videotapes and EEG data on the computer for analysis and reviewing. EEG electrodes were placed according to the international 10/20 system of EEG. Additionally, a basal ring of electrodes (S01—

S02; F11—F12; TP9—TP10, FT9—FT10) and sphenoidal electrodes were placed in order to evaluate interictal and ictal epileptic activity in temporal lobes more sufficiently. EEG analysis was performed using continuous 24 h day and night video-EEG monitoring according to therapeutic intensive seizure analysis (TISA) described by Stefan et al.[20] Epileptiform discharges (IEDs) were calculated by the number of IEDs counted on either side as a percentage of the total number of IEDs recorded on both sides. Unilateral interictal and ictal activity were defined by IEDs which showed $\geq$80% of unilateral activity. EEG analysis was performed blinded to ^{1}H-MRS.

High resolution MR imaging

MR imaging was performed at 1.5 T Siemens Magnetom Sonata (Siemens Medical Solutions, Erlangen, Germany) with a standard head coil and included the following sequences: T2w, fluid attenuated inversion recovery (FLAIR), transversal angulated (parallel to the long axis of the hippocampi; TR 10000, TE 109, slice thickness 5 mm); T2w perpendicular to the long axis of the hippocampi (TR 7420, TE 98, slice thickness 3 mm); T2*w gradient echo (FLASH; TR 858, TE 26, slice thickness 5 mm); T1w 3D gradient echo (MP Rage; 1 mm 3D-postprocessing, TR 2030, TE 3.93, matrix 256 $\times$ 256); T1w inversion recovery, perpendicular to the long axis of the hippocampus (TR 9650, TE 16, slice thickness 3 mm); T1w Gadolinium enhanced at first admittance to exclude other pathologic alterations (e.g. inflammatory disease, cavernoma). Patients with evidence for extra-hippocampal pathology were excluded. The criteria for a diagnosis of HS on MR images included the presence of unilateral atrophy and high T2w signal of the hippocampus.

Single voxel spectroscopy (SVS)

At the time of scanning, patients in both groups were seizure free for at least 3 days. All experiments were carried out using a 1.5 T Siemens Magnetom Sonata (Siemens medical solutions, Erlangen, Germany) clinical whole body MR scanner using a standard head coil. To obtain optimal signal demarcation of the hippocampus from the amygdala and avoid cerebrospinal fluid (CSF) contamination of the ventricular system sagittal, transversal and coronar T2w images in three orthogonal planes were used as localizer (Fig. 1). The voxel comprised the head and anterior body portion of the hippocampus. In order to minimize partial-volume effects, the voxel size was reduced to a minimum of 2 cc arising from an edge length of 20 mm in the sagittal axis and 10 mm in the coronal and transversal axis. In the healthy control group and in patients with no pathological findings in MRI there was no hippocampal atrophy and the voxel comprised mainly hippocampal tissue. The partial-volume effect in these groups was determined by segmenting on coronal T2w images and was less than 10% of the voxel. In patients with hippocampal atrophy due to HS CSF fraction (partial-volume effect) in the hippocampal voxel was determined by segmenting on coronal T2w images as well. The corrections of each metabolite for CSF dilution was carried out by the formula: $C_{corr} = (C_{meas} \times 100)/(100 - CSF_{perc.})$— C_{meas} refers to measured concentration of metabolite of the whole voxel, $CSF_{perc.}$ is the percentage of CSF in the voxel.

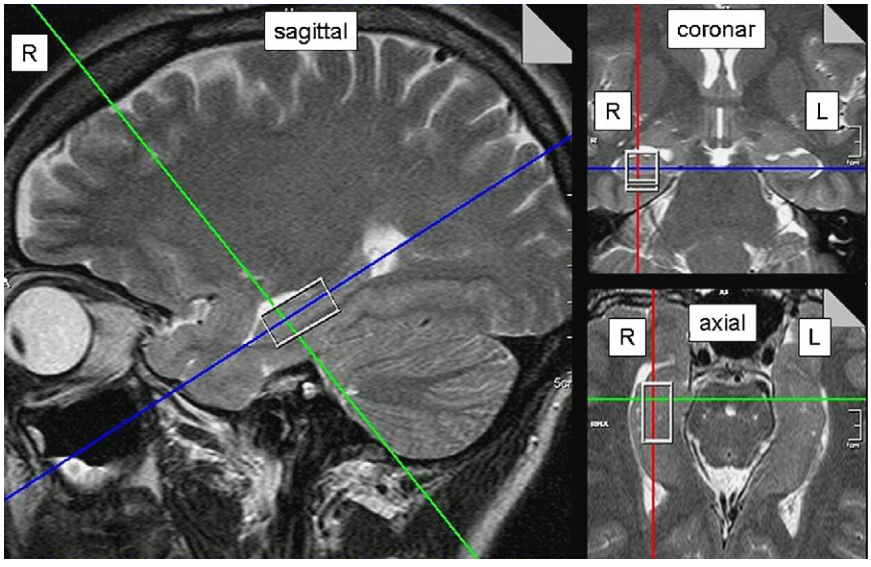

Figure 1 The MR image illustrates hippocampal voxel of interest (VOI) of ^{1}H-MRS (T2w, TR 7420, TE 98, slice thickness 3 mm).

Three ''chemical shift selective'' (CHESS) pulses prior to the ''point resolved spectroscopy'' (PRESS) were implemented for water suppression; repetition time (TR) 3000 ms; echotime (TE) 30 ms; averages 128; vector size 1024. Determination of the absolute metabolite concentrations in SVS was carried out by water scaling, a method in which the resonance area of the unsuppressed water signal is used as an internal reference. An appropriate water-unsuppressed voxel of identical voxel localization and measurement parameters was obtained for each water-suppressed voxel, differing only in the number of acquisitions that were reduced to 12. tNAA, Cho, Cr, Glx and m-Ins were quantified using LCModel,[21] which is a user-independent time domain spectral fitting program. Water scaling and fitting were carried out automatically. Spectra were not corrected for T1 saturation. All concentrations are estimated metabolite levels with an unknown degree of T1 saturation and are referred to as institutional units (arbitrary units of our institute). Estimated uncertainties by Cramer-Rao lower bounds (CRLB) served as main guidelines for judging the spectra of absolute metabolite concentrations. Only metabolite spectra with LCModel estimated uncertainty of <15% standard deviation (S.D.) of the evaluated concentrations and spectra with an SNR (signal to noise ratio) above 3 were included in this study. Spectra with a FWHM > 0.065 ppm were not included in the study. For further details see Hammen et al.[22] and Provencher and Helms et al.[21,23,24] Analysis of metabolite spectra was performed blinded to EEG and MRI results.

Statistics

Statistical analysis was carried out by SPSS 15. Normal distributions of metabolite concentrations were verified by the Kolmogorov–Smirnov test. Metabolite values were classified as pathological if the deviation from the mean of the healthy controls exceeded 2 S.D.s. Descriptive statistics (mean (M), S.D. and 95% confidence interval (95% CI)) were calculated. For statistical analysis one-way analysis of variance (ANOVA) with post hoc multiple comparisons and Bonferroni correction was applied. The statistical significance level was based on $p < 0.05$.

Results

The mean level of tNAA ipsilateral to seizure focus was significantly decreased in MRI positive- (4.59 ± 0.68) and MRI negative (5.82 ± 0.78) patients in comparison to healthy controls (6.91 ± 0.55) (ANOVA $F = 60.2$, d.f. = 2/46, $p < 0.001$, Table 1). Additionally, tNAA level of MRI positive patients was significantly reduced compared to MRI negative patients (post hoc test (Bonferroni) $p < 0.001$, Fig. 2). Fig. 3 delineates the strictly separated tNAA 95% confidence intervals of the different groups, highlighting the clear ''tNAA cut-off'' between MRI positive- and MRI negative patients and healthy controls (95% confidence intervals: MRI positive 4.25–4.95; MRI negative 5.22–6.34; healthy controls 6.67–7.12). The highest tNAA reduction compared to healthy controls was seen in the MRI positive group, a moderate but still signifi-

Table 1 Mean metabolite level ipsilateral to EEG focus in MRI positive- and MRI negative TLE patients in comparison to healthy controls (mean referred to as institutional units)

Metabolites ipsilateral to EEG focus	Groups	*N*	Mean	Standard deviation (S.D.)	95% Confidence interval (CI)		ANOVA Bonferroni corrections for five comparisons ($p = 0.01$)	
tNAA	MRI pos.	17	4.59	0.68	4.25	4.95	<0.001 *	<0.001$^{\#}$
	MRI neg.	9	5.82	0.78	5.22	6.43	<0.001 *	
	controls	21	6.91	0.55	6.67	7.12		
Glx	MRI pos.	17	9.74	2.09	8.47	11.00	ns *	
	MRI neg.	9	11.10	2.33	9.31	12.89	ns *	
	controls	21	9.45	1.56	8.74	10.16		
m-Ins	MRI pos.	17	5.78	1.36	5.05	6.50	ns *	
	MRI neg.	9	5.47	1.31	4.38	6.57	ns *	
	Controls	21	4.98	0.86	4.59	5.37		

Statistical evaluation demonstrated significant tNAA reduction in MRI positive- and MRI negative patients in comparison to healthy controls (*$p < 0.001$). Additionally, tNAA level of MRI positive patients was significantly reduced compared to MRI negative patients ($^{\#}p < 0.001$). Increase of Glx level in MRI negative- and m-Ins level in MRI positive patients in comparison to healthy controls did not reach statistical significance ($p > 0.05$). No statistical significance in group comparison of mean ipsilateral Cho and Cr was noticed (results not included in Table 1). One-way analysis of variance (ANOVA); MRI pos., MRI positive patients; MRI neg., MRI negative patients; *N*, patient numbers; ns, not statistically significant ($p > 0.05$); *in comparison to healthy controls; $^{\#}$MRI positive vs. MRI negative patients.

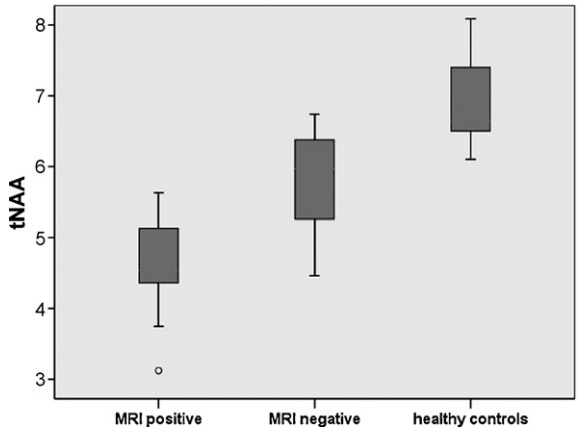

Figure 2 Group comparison of tNAA levels ipsilateral to EEG focus (box plot). The lowest tNAA levels were noticed in the MRI positive group. Nevertheless, MRI negative patients also displayed significantly reduced tNAA levels ($p < 0.05$) in comparison to healthy controls (*Y*-axis = institutional units).

cant reduction of tNAA was noticed in the MRI negative group.

All MRI positive patients showed ipsilateral tNAA reduction exceeding 2 S.D. compared to healthy controls. Six out of nine MRI negative patients demonstrated a reduction of more than 2 S.D. of tNAA.

Mean Glx level ipsilateral to seizure focus in MRI negative patients (11.10 ± 2.33) was increased compared to the MRI positive patients (9.74 ± 2.09) and healthy controls (9.45 ± 1.56) (Fig. 4). However, only two out of nine MRI negative patients showed a significant elevation of more than 2 S.D. of Glx. Results did not reach statistical significance using

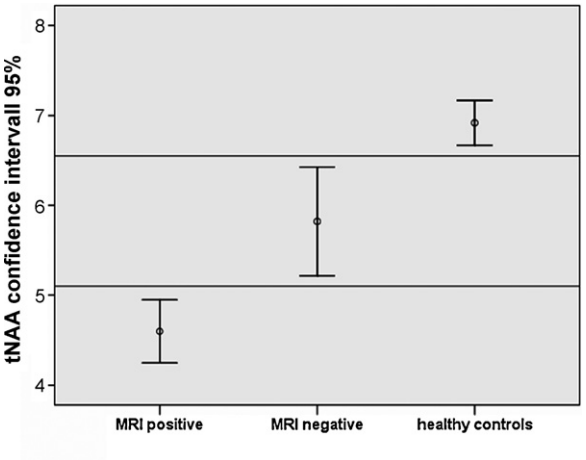

Figure 3 This graphic delineates that alterations in spectral tNAA can distinctively be assigned to the different groups (95% confidence interval—MRI positive, MRI negative and healthy controls). Our results demonstrate a clear "tNAA cut-off" between the three groups.

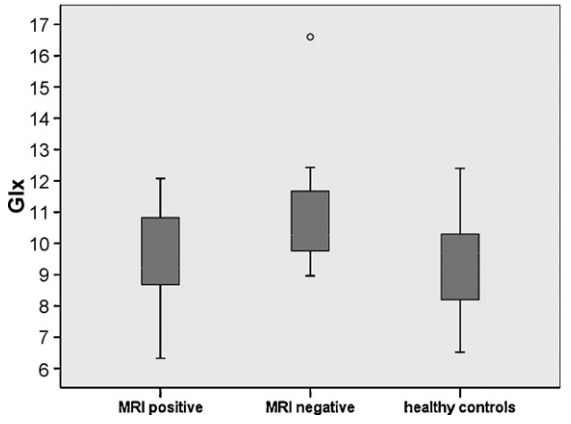

Figure 4 Group comparison of Glx levels ipsilateral to EEG focus (box plot). In the MRI negative group mean Glx level was not significantly elevated ($p > 0.05$), however, in individual cases a significant elevation was noticed.

ANOVA with Bonferroni corrected post hoc multiple comparisons.

Mean m-Ins level ipsilateral to seizure focus was increased in MRI positive patients (5.78 ± 1.36) compared to MRI negative patients (5.47 ± 1.31) and healthy controls (4.98 ± 0.86) (Fig. 5). However, only 4 out of 17 MRI positive patients showed a significant elevation of more than 2 S.D. of m-Ins. Results did not reach statistical significance using ANOVA.

No statistical significance in-group comparison of mean ipsilateral Cho and Cr was noticed.

Contralateral tNAA reduction was found in 22% (2/9) in the MRI negative group versus 18% (3/17) in MRI positive patients. Other contralateral metabolites were within the normal range, apart from increased Glx level in one MRI negative patient.

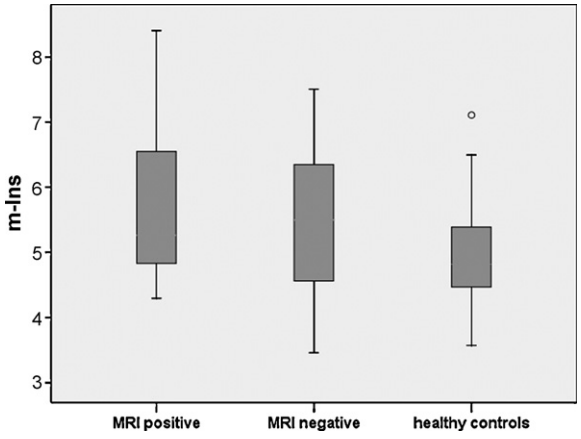

Figure 5 Group comparison of m-Ins levels ipsilateral to EEG focus (box plot). In the MRI positive group mean m-Ins level was not significantly elevated ($p > 0.05$), however in individual cases a significant elevation was noticed.

Discussion

Total NAA level has the lowest variation coefficient of all detectable brain metabolites.[22] It is decreased ipsilateral to lesion, respectively EEG focus in TLE patients with evidence for HS,[1,2,11,17,25] which is either due to neural cell loss or neuronal dysfunction.[6,8,10,12–14,26] In patients with HS reduction of tNAA can partially be explained with neural loss as it is believed to be located primarily within neurons.[11,27,28] The question how epileptic discharges in TLE patients with normal findings in MRI are related to marginal neuronal loss or metabolic dysfunction still remains unclear.

To our knowledge this is the first study that highlights a clear "tNAA cut-off" between MRI positive- and MRI negative patients and healthy controls. However, Woermann et al.[11] reported that the decrease of NAA was less marked in MRI negative hippocampi on the side of seizure onset than in HS. Fig. 3 delineates that alterations in spectral tNAA can distinctively be assigned to the different groups (95% confidence interval). Despite the limited patient numbers the distinct "tNAA cut-off" between the groups is remarkable. The highest degree of tNAA reduction compared to healthy controls was seen in the MRI positive group (Figs. 2 and 3). A moderate but still significant reduction of tNAA was noticed in the MRI negative group. The minor degree of tNAA reduction in the MRI negative group may be attributed to a minor lesion of unknown underlying cause, respectively initial disease stage. This leads to functional deficit and not to lesional findings detectable by imaging modalities as MRI.[7] In further progress disease alterations become more pronounced, visible in MRI as lesions and easier to detect in ^{1}H-MRS and multimodal imaging (e.g. single photon emission computed tomography (SPECT) and positron emission tomography (PET)).[9,29] In this case high field MRI of 3 T or above and different contrast type might be able to detect more subtle tissue pathology.

Several studies have addressed the role of spectral metabolite markers using histopathological correlations.[30,31] The correlation between spectral metabolite alterations (tNAA) and the degree of neuronal loss was confirmed by Duc et al.[1] In vitro ^{1}H-MRS of hippocampal specimen at 11.75 T did not reveal a significant association between hippocampal neuron loss and cellular content of tNAA.[13] Therefore, the reduction of tNAA was attributed to neuronal dysfunction caused by compromised mitochondrial pathways.

Glx consists of glutamine and glutamate which are present in both neuronal and in glial cells. With 1.5 T scanners separation of glutamine and glutamate peaks is not possible, thus the mechanisms underlying the elevated Glx level in individual cases of MRI negative patients in our study and in other studies[11] must be speculative. In our study mean Glx level in the MRI negative group was not significantly elevated after Bonferroni corrected post hoc multiple comparisons. High intracellular glutamate concentrations or elevated release of glutamate could contribute to increased electrical irritability, respectively promoting excitotoxicity.[11,14,32,33] Owing to conversion of glutamate to glutamine in astrocytes, energy failure due to hampered mitochondrial respiration und ATP synthesis might lead to accumulation of intracellular glutamate. Additionally, possible high levels of extracellular Glx arise. Further studies are needed to evaluate this issue, particularly because there has been some discrepancy concerning elevated Glx levels in TLE patients.[4,11,14,15,17,25]

Alike to Glx the role of m-Ins remains controversy. Wellard et al.[4] reported elevated m-Ins in the epileptogenic temporal lobe of patients with HS. He concluded that m-Ins changes may distinguish between the seizure focus, where m-Ins is increased and areas of seizure spread like in the frontal lobe where m-Ins is decreased. This might help to distinguish drug refractory TLE patients, who will benefit from surgery by excluding bilateral foci which is of importance for predicting postoperative outcome.[9,12,34–36] Contrary to these results, Riederer et al.[17] and Mueller et al.[19] reported lower m-Ins levels in patients with mesial TLE. In our study mean m-Ins level was not significantly elevated or reduced after Bonferroni corrected post hoc multiple comparisons, however in individual cases a significant elevation was noticed in the MRI positive group. Cerebral m-Ins concentrations are possibly affected through seizures and antiepileptic drug treatment which might explain contradictory results.[17,37,38] Therefore, as concluded by Riederer et al.[17] the relation between epilepsy and m-Ins has to be investigated in other models.

Conclusion

MRI negative TLE patients have a different MRS profile than MRI positive patients (HS) with marginal but significant decrease of tNAA. Our results highlight a clear "tNAA cut-off" (95% confidence interval) between the groups. The minor degree of tNAA reduction in the MRI negative group may be attributed to minor lesions of unknown underlying cause. This leads to functional deficit and not to lesional findings. Higher field MRI of 3 T or above might be able to detect more subtle tissue pathology. The

value of m-Ins and especially Glx in MRI negative TLE patients remains controversy. Adequate statistical analysis and larger patient numbers are necessary as demonstrated in this study.

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