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Magnetic resonance spectroscopy of the thalamus in patients with mesial temporal lobe epilepsy and hippocampal sclerosis

Dagmar Fojtiková[1*], Milan Brázdil[1], Antonín Škoch[2*], Filip Jírů[2*], Jaroslav Horký[3], Radek Mareček[1], Michal Mikl[1], Petr Krupa[4]

[1] Brno Epilepsy Centre, Department of Neurology, St. Anne's University Hospital, Brno
[2] MR Unit, Department of Diagnostic and Interventional Radiology, Institute for Clinical and Experimental Medicine, Prague
[3] Department of Nuclear Magnetic Resonance, Institute of Scientific Instruments, Academy of Sciences, Brno
[4] Department of Neuroimaging, St. Anne's University Hospital, Brno, Czech Republic

ABSTRACT – *Purpose:* to investigate potential neuronal dysfunction within the thalamus in patients suffering from mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE/HS). *Methods:* we examined twenty epileptic patients suffering from mesial temporal lobe epilepsy with hippocampal sclerosis (17 females, 3 males) and twenty sex- and age-matched healthy controls. H MR spectroscopic imaging (SI) was performed over the right and left thalamus in all patients and controls. In addition both hippocampi were investigated by the H MR spectroscopic single voxel (SV) technique in both groups. *Results:* statistical analysis of compared data in both groups demonstrated that the total thalamic NAA level was significantly decreased in patients with MTLE/HS as compared to healthy controls. Detailed analysis revealed a statistically significant reduction of NAA, NAA/Cr and NAA/(Cr+Cho) ratios in the thalamus ipsilateral to hippocampus affected with hippocampal sclerosis in patients compared to controls, while no significant changes were observed in the thalamus contralateral to sclerotic hippocampus. A comparison of values in ipsilateral and contralateral thalami in patients showed statistically significant difference with lower values of NAA and both ratios in the ipsilateral thalamus. Previously reported reduced hippocampal concentration of NAA, NAA/Cr and NAA/(Cr+Cho) ratios on the side of hippocampal sclerosis compared with contralateral hippocampus in patients and both hippocampi in controls was confirmed. *Conclusions:* the present MRS data clearly indicate neuronal dysfunction within the thalamus ipsilateral to the sclerotic hippocampus of patients with mesial temporal lobe epilepsy. In agreement with other recent functional and structural neuroimagings our results confirm the role of the ipsilateral thalamus in the medial temporal/limbic epileptic network.

Key words: mesial temporal lobe epilepsy, proton magnetic resonance spectroscopy, thalamus, epileptic network

Correspondence:
D. Fojtiková, MD,
Department of Neurology,
Masaryk University,
St. Anne's University Hospital, Pekařská 53,
656 91 Brno, Czech Republic
<dagmar.fojtikova@centrum.cz>

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* These three authors contributed equally to this work.

Hippocampal sclerosis is the most commonly observed and well-known pathology in pharmacologically intractable temporal lobe epilepsy. However, there is a considerable amount of compelling evidence from clinical and pathological studies that there is an epileptic network of tightly connected cortical and subcortical brain structures that are involved in epileptic activity and that are impaired in patients with refractory mesial temporal lobe epilepsy. It was assumed that this epileptic network as a whole is responsible for the manifestation of seizures in temporal lobe epilepsies. From this idea is derived the important issue that interruption of the network activity by electrical, biochemical, or metabolic influences in any part of the network will alter seizure expression or its occurrence (Spencer 2002). As a hypothetical part of this medial temporal/limbic epileptic network, the thalamus has well-developed anatomic connections with mesial temporal lobe structures.

The role of the thalamus has been studied predominantly in idiopathic generalized epilepsy (IGE). In several subtypes of IGE neuronal impairment within the thalamus has been indicated by MR spectroscopy, and consistently described in recently published MRS studies. (Bernasconi *et al.* 2003a; Mory *et al.* 2003; Savic *et al.* 2004; Fojtikova *et al.* 2006). However there is also increasing evidence concerning participation of the thalamus in focal epilepsies. Alteration in the subcortical regions has been demonstrated in patients with temporal lobe epilepsy by using various functional and structural imaging methods, including positron emission tomography (FDG-PET) (Henry *et al.* 1990; Arnold *et al.* 1996; Juhasz *et al.* 1999; Newberg *et al.* 2000; Benedek *et al.* 2004), single-photon emission computed tomography (SPECT) (Yune *et al.* 1998; Shin *et al.* 2001; Tae *et al.* 2005), MRI volumetry (Bonilha *et al.* 2003; Bernasconi *et al.* 2004; Natsume *et al.* 2003) and voxel-based morphometry (VBM) (Keller *et al.* 2002; Keller *et al.* 2004; Bernasconi *et al.* 2004).

The current research study was carried on to investigate the potential involvement of thalamic structures in the pathogenesis of seizures in mesial temporal lobe epilepsy by magnetic resonance spectroscopy (MRS). Our aim was to analyse possible neurochemical changes within this structure. We hypothesized that the concentration of thalamic NAA might be lower in investigated patients than in healthy control subjects. The assumed reduction was suggested to be mainly in the thalamus ipsilateral to the affected hippocampus.

Materials and methods

Subjects

Twenty MTLE/HS patients from our fourth level surgical centre for epilepsy were admitted to the study. We analysed the data of 20 consecutive adult patients (17 females, 3 males) in whom we had recorded temporal lobe seizures during their video EEG monitoring and those who fulfilled the diagnostic criteria for mesial temporal lobe epilepsy with hippocampal sclerosis. The control group consisted of twenty sex- (17 females, 3 males) and age-matched healthy volunteers. The mean age of the subjects in the patient group was 38.9 ± 9.7 years (ages ranged from 17 to 55 years; median 38.5 years); the mean age in the control group was 38.4 ± 7.9 years (ages ranged from 18 to 51 years; median 39 years). All of the patients had been routinely investigated, including long-term semi-invasive video-EEG monitoring, high resolution MRI, and neuropsychological testing. The diagnosis of mesial temporal lobe epilepsy in our patients was based on a consonance of history data, ictal and interictal EEG findings, ictal semiology, neuropsychology, interictal SPECT/PET and neuroimaging findings. Visual inspection of the MRI scans, by two independent physicians (radiologist and epileptologist), revealed unequivocal unilateral hippocampal sclerosis; in 14 patients on the left side and in 6 patients on the right side. All of our patients had MRI evidence of unilateral hippocampal sclerosis concordant with the EEG lateralizaton of the epileptogenic zone. None of our patients revealed other brain structural lesions on MRI scans and none of the patients had undergone previous intracranial surgery. The mean age of the patients at the time of seizure onset was 9.7 ± 9.8 years; with a median 7.5 years. The mean value of duration of the disease in the patient group was 28.3 ± 13.7 years; with a median 30 years. According to a history data (seizure diary), the complex partial seizure frequency ranged from 1 to 25 seizures per month, with a mean of 6.1 ± 5.3 seizures per month. The frequency of secondary generalization of their seizures (sGTCS) ranged from 0 to 5 seizures per month, with a mean of 0.7 ± 1.7 seizures per month. All patients had been seizure free for ≥ 24 hours before MRS investigation.

The majority of the healthy subjects in the control group were volunteers from the professional sector with no history of neurological or psychiatric diseases. Informed consent was obtained from each participant after all of the procedures were fully explained. The study received the approval of the local ethics committee.

MRS measurement

MR examinations were performed on a 1.5 T scanner (Siemens Symphony, Erlangen, Germany) using a multi channel head coil. The MRI protocol included 3D T_1-weighted magnetization prepared rapid gradient echo (MR RAGE) images (TE/TR = 3.93/1 700 ms) and T_2-weighted turbo spin echo images (TE/TR = 108/4 560 ms) in the coronal and transversal planes.

The protocol for spectroscopic examination included proton single voxel spectroscopy (SVS) and spectroscopic imaging (SI). SVS was measured using the PRESS sequence from the left and right hippocampus with the following parameters: TR = 1 500 ms; TE = 80 ms; number of aver-

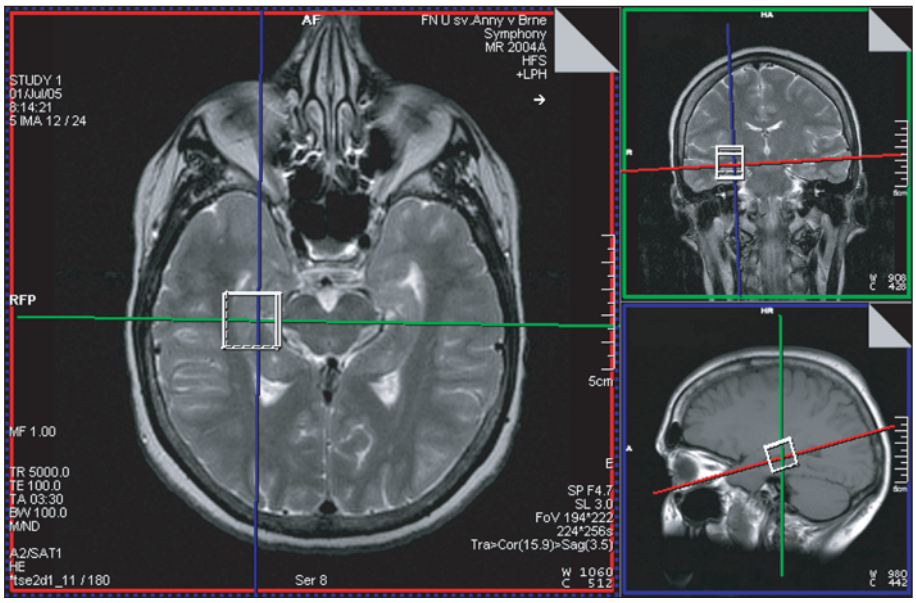

Figure 1. Proton magnetic resonance spectroscopy of the hippocampus. T2-weighted image in the transversal plane, placement of the volume of interest (VOI) over the right hippocampus; a single voxel spectroscopy method. On the right side T2-weighted image in the coronal plane, underneath high-resolution anatomical T1-weighted image in the sagittal plane; both images with the placement of VOI over the right hippocampus.

ages 128; VOI (volume of interest) size 20 x 20 x 20 mm; 1 024 time points and bandwidth 1 000 Hz. The VOI included part of the head and the mid region of the left and right hippocampus as shown in *figure 1*. Both water suppressed spectra and spectra without water suppression (32 averages) were acquired.

SI was measured using the volume pre-selected PRESS-SI sequence from both thalami with the following parameters: TR = 1 500 ms; TE = 80 ms; number of averages = 12; FOV (field of view) 80 x 80 mm; VOI = 40 x 40 mm; slice thickness = 10 mm; 8 x 8 elliptically weighted (hamming weighting) encoding steps; 1 024 time points and bandwidth 1 000 Hz. Both water suppressed SI spectra and SI spectra without water suppression (4 averages) were acquired. The exact positioning of the VOI was adjusted according to the individual anatomy using MRI images *(figure 2)*.

Data processing and evaluation

SI spectra were first zero filled to a 16 x 16 matrix arriving at the final a nominal voxel size of 5 x 5 x 10 mm. No additional k-space filtering was performed.

Both SVS and SI data were processed by the LCModel (Provencher 1993) using water as an internal standard (Gasparovic *et al.* 2006) accounting for the different water content in white matter (WM), grey matter (GM) and cerebrospinal fluid (CSF) as well as for the different point spread functions in T_1-weighted MP RAGE images and SI data. Concentration values of water in individual tissue types and the corresponding water relaxation times were adopted from (Gasparovic *et al.* 2006). Calculated concentrations of individual metabolites evaluated by the LCModel were further corrected for metabolites' relaxation times T1 and T2. T1 and T2 values for the hippocampus were adopted from Christiansen *et al.* (1993), T1 and T2 values for the thalamus from (Frahm *et al.* 1989). All SI data calculations and corrections were performed using the LCModel - SI data interface CULICH (Jiru *et al.*).

For the evaluation of metabolite concentrations from SI data 4 adjacent voxels situated in the centre of the right and left thalamus were selected *(figure 2)*. All selected voxels were located entirely within the thalamus to minimize partial volume effects.

For statistical analysis values of NAA, NAA/Cr and NAA/(Cr+Cho) ratios were used. The obtained values were compared between the thalami of patients and controls and between the hippocampi of patients and controls.

Statistical analysis

To evaluate the differences in the NAA, NAA/Cr and NAA/(Cr+Cho) ratio of the determined hippocampal and thalamic voxels, a t-test was performed to compare the patients and the healthy controls. The values of the NAA, NAA/Cr and NAA/(Cr+Cho) were analysed separately for the affected (with hippocampal sclerosis) and non-affected (without hippocampal sclerosis) hippocampi in patients and together for the controls (right and left hippocampi together). The same approach was used for assessment of

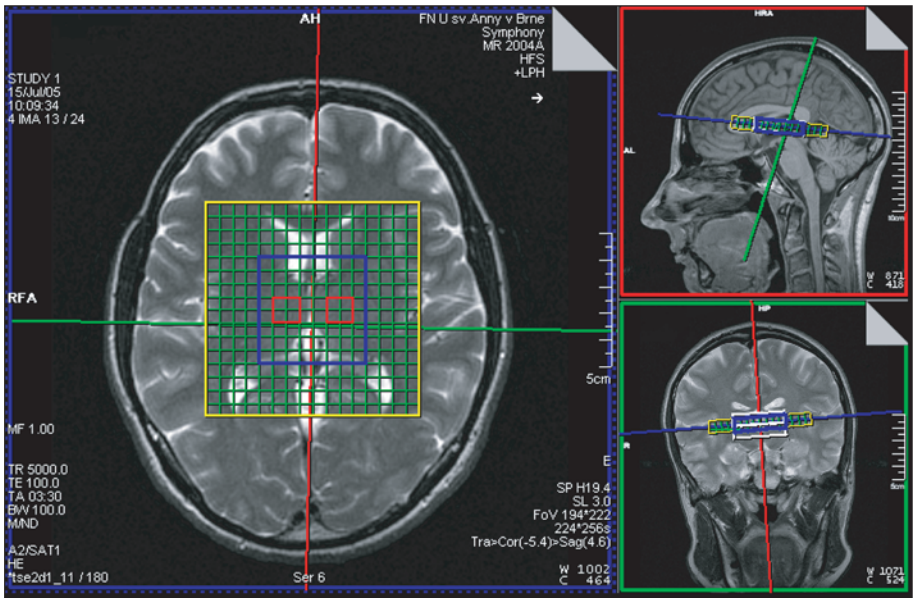

Figure 2. Proton magnetic resonance spectroscopy of the thalamus. T2-weighted image in the transversal plane. Placement of the volume of interest (VOI) over the right and left thalami; a spectroscopic imaging (SI) method. Graphic demonstration of 4 selected voxels (outlined with red in the centre of both thalami) for further statistical analysis. On the right side high-resolution anatomical T1-weighted image in the sagittal plane and T2-weighted image in the coronal plane with positioning of the VOI over the thalami.

the ipsilateral (ipsilateral to the affected hippocampus) and contralateral (contralateral to the affected hippocampus) thalami in patients and both thalami together in controls. Prior to the use of the t-test, the normal distribution of the values in patients and in healthy controls was verified. Statistical significance was considered to be present if $p < 0.05$ in all tested parameters.

The Pearson correlation was computed between the clinical variables (demographic data: duration of epilepsy, age of seizure onset and frequency of seizures in the patient group) and spectroscopic data of thalami and hippocampi. In addition the Pearson correlation was performed to study the potential relationship between the spectroscopic data of the thalamus and the estimated number of lifetime generalized seizures.

The Statistica program from StatSoft was used for data analysis.

Results

Patients and healthy controls did not differ with respect to age (patient group with a mean age of 38.9 years, SD = 9.7 years; healthy controls with a mean age of 38.4 years, SD = 7.9; $p = 0.83$).

The mean values of our final data of the NAA, NAA/Cr and NAA/(Cr+Cho), shown separately for the ipsilateral and contralateral thalami (to affected hippocampus) in a patient group and bilateral for the controls, are given in *table 1*.

Statistical analysis of compared data in both groups demonstrated that the total (ipsilateral and contralateral) thalamic NAA was significantly decreased in patients with MTLE/HS as compared to healthy controls ($p = 0.02$), in NAA/(Cr+Cho) the ratio p value was bordering statistical significance ($p = 0.06$), while no significant differences were observed in NAA/Cr ratio ($p = 0.19$).

Table 1. Mean values of analysed parameters separately for ipsilateral and contralateral thalamus in patients and together for right and left thalamus in controls.

	Ipsilateral		Contralateral		Controls (R + L)	
	Mean	Std. Dev.	Mean	Std. Dev.	Mean	Std. Dev.
NAA	16.273	1.971	17.673	2.765	17.639	2.413
NAA/Cr	1.120	0.174	1.200	0.191	1.207	0.164
NAA/(Cr+Cho)	0.907	0.134	0.976	0.148	0.993	0.134

Ipsilateral = ipsilateral thalamus to affected hippocampus in patients; contralateral = contralateral thalamus to affected hippocampus in patients; R = right thalamus in controls; L = left thalamus in controls.

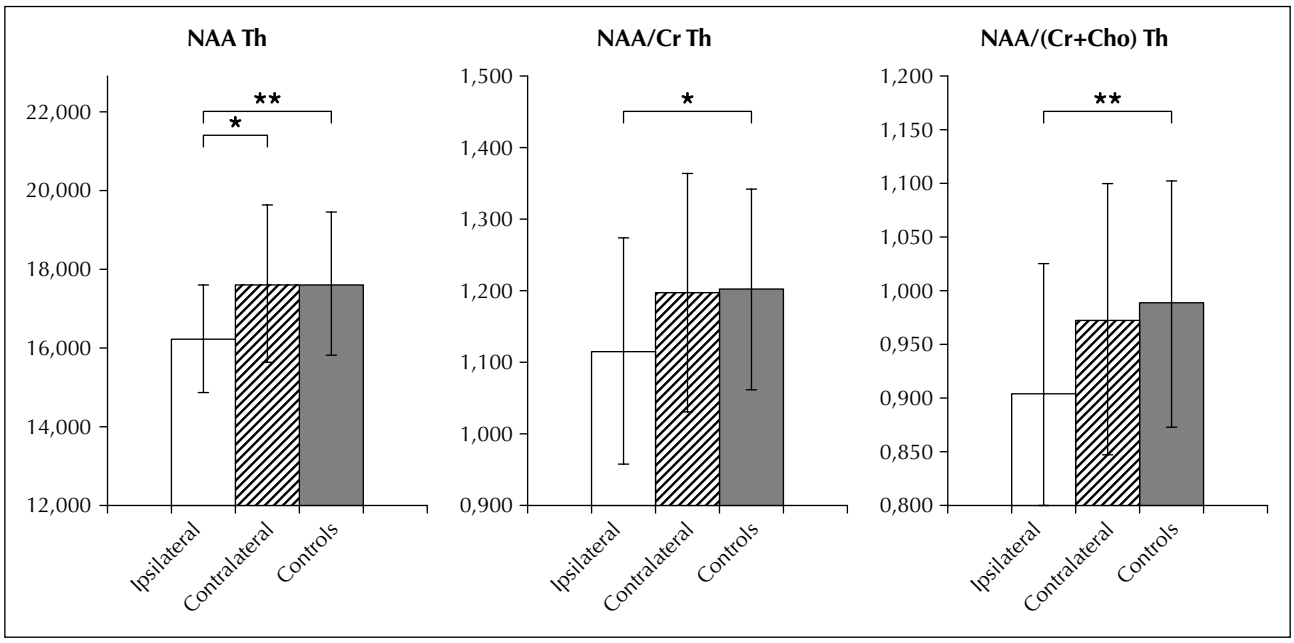

Figure 3. Comparison of values in ipsilateral and contralateral thalami in patients showed statistically significant difference with lower values of NAA and NAA/Cr and NAA/(Cr+Cho) ratios in ipsilateral thalamus to affected hippocampus. A statistically significant reduction of presented parameters was also revealed in the ipsilateral thalamus in patients compared to controls, while no significant changes were observed in the thalamus contralateral to the sclerotic hippocampus.
Th = thalamus; * $p < 0,05$; ** $p < 0,01$.

When comparing the symmetry of the analysed parameter's distribution between ipsilateral and contralateral thalami in patients, the t-test showed statistically significant asymmetry with lower values in the ipsilateral thalami in all tested parameters; NAA ($p < 0.001$), NAA/Cr ($p = 0.006$) and NAA/(Cr+Cho) ratio ($p = 0.003$).

When comparing values from ipsilateral and contralateral thalami separately between patients and controls, the t-test showed significantly lower values in the ipsilateral thalami in NAA, NAA/Cr and NAA/(Cr+Cho) in our epilepsy patients (with $p < 0.001$ in all parameters), while no statistically significant differences were observed between the contralateral thalamus of patients and both thalami of controls *(figure 3)*.

The mean values of analysed data of hippocampal NAA, NAA/Cr and NAA/(Cr+Cho), separately for the affected (with hippocampal sclerosis) and non-affected (without hippocampal sclerosis) hippocampus in a patient group and together for the controls, are given in *table 2*.

The hippocampal values were significantly reduced in the affected hippocampus of patients in comparison with both hippocampi of controls in all tested parameters; $p < 0.001$. A statistically significant difference was also revealed between the non-affected hippocampus of patients and both hippocampi of controls in NAA value ($p = 0.001$), while no significant differences were observed in NAA/Cr and NAA/(Cr+Cho) ratios.

A statistical comparison of the NAA, NAA/Cr and NAA/(Cr+Cho) ratio between the affected and non-affected hippocampus in our patient group showed significantly lower values in the sclerotic hippocampus; NAA ($p = 0.006$), NAA/Cr ($p = 0.007$) and NAA/(Cr+Cho) ratio ($p = 0.006$) *(figure 4)*.

Table 2. Mean values of analysed parameters separately for affected and non-affected hippocampus in patients and together for right and left hippocampus in controls.

	Affected		Non-affected		Controls (R + L)	
	Mean	Std. Dev.	Mean	Std. Dev.	Mean	Std. Dev.
NAA	9.547	0.971	10.366	0.808	11.126	0.808
NAA/Cr	0.800	0.117	0.903	0.110	0.909	0.100
NAA/(Cr+Cho)	0.641	0.090	0.722	0.087	0.735	0.078

Affected = hippocampus with hippocampal sclerosis in patients; non-affected = healthy hippocampus in patients; R = right hippocampus in controls; L = left hippocampus in controls.

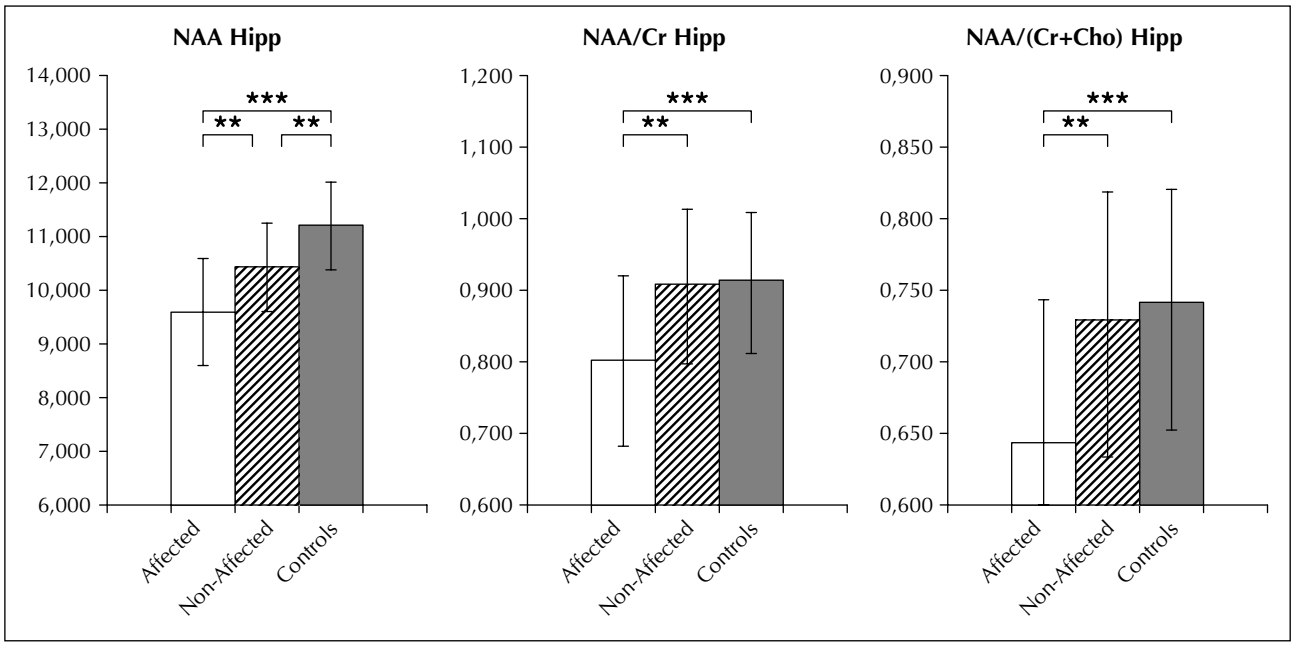

Figure 4. A statistical comparison of the NAA, NAA/Cr and NAA/(Cr+Cho) ratios between the affected and non-affected hippocampus in our patient group showed significantly lower values in the affected hippocampus. A statistically significant difference was also revealed between non-affected hippocampus of patients and both hippocampi of controls in NAA value, while no significant differences were observed in NAA/Cr and NAA/(Cr+Cho) ratios.
Hipp = hippocampus; ** $p < 0,01$; *** $p < 0,001$.

In our data, no significant correlation was found between clinical variables (duration of epilepsy, age of seizure onset and frequency of seizures) and spectroscopic values (NAA and both ratios) from each side of the thalami and hippocampi in the patient group. There was also no significant correlation found between MRS data of the ipsilateral and contralateral thalami and frequency of secondarily generalized seizures.

Discussion

A remarkable amount of convincing evidence for the existence of specific cortical and subcortical networks in the genesis and expression of partial and generalized seizures exists in animal and experimental models. A network is considered to be a set of specific brain structures and regions, anatomically and functionally connected, in which activity in any one part affects activity in all the others. An assumed network, associated with the most common human intractable epilepsy – temporal lobe epilepsy, represents the medial temporal/limbic network. This network includes the hippocampi, the amygdalae, the entorhinal cortices, lateral temporal neocortices, and extratemporal components consisting of the thalamus and frontal lobes. The network as a whole is thought to be responsible for the development and manifestation of the seizures (Spencer 2002).

Functional and structural neuroimaging has been very influential in demonstrating alterations in temporal and extratemporal structures in temporal lobe epilepsy. These findings are particularly valuable, as it is difficult to obtain ictal or interictal EEG activity from many parts of the human brain, especially from subcortical structures. In humans, functional studies repeatedly linked cortical epileptogenic zones and subcortical nuclei.

The interictal hypometabolism in the striatum and the thalamus ipsilateral to the epileptogenic temporal lobe was found in patients with intractable TLE (Sperling *et al.* 1990) and this link was confirmed in other studies (Henry *et al.* 1993; Juhasz *et al.* 1999; Henry *et al.* 1990; Arnold *et al.* 1996). Decreased thalamic cerebral blood flow measured by xenon CT (Kashiwagi *et al.* 1993) was found ipsilateral to the cortical seizure focus in TLE patients. Ictal SPECT studies have also helped to demonstrate the participation of the ipsilateral thalamic region in the medial temporal lobe limbic network (Berkovic *et al.* 1992; Zubal *et al.* 1995; Markand *et al.* 1995; Yune *et al.* 1998; Tae *et al.* 2005). A recent study in patients with hippocampal sclerosis investigated by 31P MR spectroscopic imaging, showed decreased PCr/ATP in both hippocampi, ipsilateral thalamus and striatum, suggesting that the linked metabolic balance is altered. (Pan *et al.* 2005). Furthermore, there exists a report that hippocampal cell density is significantly correlated with the amount of reduction in

metabolism in bilateral thalamus and ipsilateral basal ganglia (Dlugos *et al.* 1999). It was postulated that this may reflect the loss of synaptic and polysynaptic connections between the mesial temporal lobe and the thalamus and basal ganglia. Hippocampal cell loss may result in decreased efferent synaptic activity from the hippocampus to the thalamus and basal ganglia, causing decreased neuronal activity in these structures with consequent hypometabolism. In turn, reduced output from the thalamus and basal ganglia may lead to increased cortical excitability (Dlugos *et al.* 1999; Mueller *et al.* 2006).

The brain was found to have a peculiarly strong correlation between function (behaviour) and structure (anatomy). In agreement with the suggestion, the functional neuroimaging goes hand in hand with structural neurofindings. Indeed the brain atrophy in patients with mesial temporal lobe epilepsy is not solely confined to the hippocampus, but extends to other brain regions. Volume loss was found in the structures surrounding the hippocampus - such as the parahippocampal region (Bernasconi *et al.* 2000; Bonilha *et al.* 2003), amygdala (Bernasconi *et al.* 1999; Guerreiro *et al.* 1999; Cendes *et al.* 1993), entorhinal (Bernasconi *et al.* 2003b) and perirhinal cortex (Jutila *et al.* 2001), the lateral temporal lobe (Moran *et al.* 2001) and interestingly significant atrophy was also observed outside of the temporal lobe throughout other regions of the limbic system (Oikawa *et al.* 2001). The thalamus (DeCarli *et al.* 1998) and caudate nucleus, predominantly ipsilateraly to the seizure focus, exhibit a significant volume reduction in patients with mesial temporal lobe epilepsy (Natsume *et al.* 2003; Dreifuss *et al.* 2001). Also a recent VBM study (Bonilha *et al.* 2005) demonstrated that the thalamic atrophy is most intense within the anterior portion of the thalamus, which has strong connections with the limbic hippocampus. It was suggested that thalamic atrophy reflects this region's anatomical and functional association with the limbic system and the authors have corroborated the hypothesis that the impairment in the brain of patients with mesial TLE follows a route according to a neural network of hippocampal and limbic connections. Thalamic atrophy, examined by MRI volumetry, was even reported in a group of patients with nonlesional TLE, again ipsilateral to the seizure focus (Natsume *et al.* 2003). Despite some discrepancies in volumetric (Bonilha *et al.* 2003; Bernasconi *et al.* 2003b) and VBM (Keller *et al.* 2004; Keller *et al.* 2002; Bernasconi *et al.* 2004) research studies, it was confirmed that hippocampal pathology in TLE is accompanied by widespread structural impairment. Furthermore a significant correlation between hippocampal and limbic system atrophy (including parahippocampal region, cingulate gyrus, basal forebrain, thalamic nuclei, medial orbitofrontal areas and the insula) in temporal lobe epilepsy has been proved in a recent study (Duzel *et al.* 2006).

Our analysis of spectroscopic images acquired with the multivoxel proton MRS technique revealed a significant reduction in the thalamic NAA, NAA/Cr and NAA/(Cr+Cho) ratios in our group of patients with MTLE/HS. Our findings support functional and supposedly also anatomical association of this region with the medial temporal/limbic system and we acknowledge the hypothesis that the damage in the brains of patients with mesial TLE follows a route according to a neural path of the temporal/limbic network. Metabolic reduction in the ipsilateral thalamus suggests the impairment of the assumed temporal/limbic network on the side of hippocampal pathology, which is fully consistent with previous imaging and functional studies mentioned above. In general, we believe that our results, which demonstrate a reduction in absolute NAA concentration and reduction in NAA/Cr and NAA/(Cr+Cho) ratios, reflect neuronal and/or axonal loss, loss of neuron viability, and neuronal dysfunction. Whether the reduction represents an irreversible loss of cells or a potentially reversible metabolic process cannot readily be determined from this study. From functional and structural neuroimaging studies the presence of abnormalities in the temporal/limbic network has been suggested to be the structural as well as functional basis. As far as we are aware, this is the first study investigating neurochemical changes of the thalamus in temporal lobe epilepsy patients by proton magnetic resonance spectroscopy. The metabolic reduction was found to be statistically significant in ipsilateral thalamus in patients and was clearly reflected in all the above tested parameters. These changes may be either a result of secondary damage from repetitive seizure activity due to excitotoxic effects or possibly a reflection of primary underlying pathology and/or due to deafferentation as a consequence of reduced efferent neurons in the epileptogenic hippocampus (Mueller *et al.* 2006).

In our present study, unexpectedly, there was neither a statistically significant correlation between ipsilateral and contralateral thalamic or hippocampal NAA, NAA/Cr and NAA/(Cr+Cho) ratios and the duration of epilepsy, nor a correlation with the seizure frequency or age of disease onset observed. There was also no significant correlation found between MRS data of the thalamus and frequency of secondarily generalized seizures. Obversely, in an FDG-PET study significantly lower thalamic metabolism in patients with secondarily generalized seizures compared with patients without secondary generalization was found (Benedek *et al.* 2004). We can speculate that the absence of described correlations in our study is due to the small set of values obtained.

In conclusion, our presented findings are consistent with the increasing evidence of an important role of the thalamus as a part of the underlying substrate, in the pathogenesis of mesial temporal lobe seizures and support the notion of a common pathophysiological network. The possible alteration of neuronal pathways in the medial temporal/limbic network seems to play a role in the epi-

leptogenesis of this most common focal epilepsy. This fascinating issue remains a target for further studies. □

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