



Quantitative MR spectroscopy reveals metabolic changes in the dorsolateral prefrontal cortex of patients with temporal lobe epilepsy

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Abstract

Objective To characterize possible metabolic changes of the dorsolateral prefrontal cortex (DLPFC) in patients with temporal lobe epilepsy (TLE).

Methods Quantitative proton magnetic resonance spectroscopy (1H-MRS) studies were performed on 24 TLE patients and 22 healthy controls. Metabolite concentrations were calculated using a linear combination model (LCModel) and corrected for cerebrospinal fluid contamination. Comparisons were performed between the TLE patients and the controls and between the left DLPFC and right DLPFC in each group. Pearson correlation coefficients were calculated between the metabolite concentrations and epilepsy duration and between the metabolite concentrations and voxel tissue composition: [gray matter (GM)/(GM+white matter (WM))].

Results Metabolic asymmetry was found in controls between the left and right DLPFC, i.e., the NAA concentration of the left DLPFC was significantly higher than that of the right. However, such metabolic asymmetry was not observed in TLE patients. Compared with the controls, TLE patients showed significantly decreased NAA and Ins, and the reductions were greater in the left DLPFC. No significant correlation was found between the metabolite concentrations and epilepsy duration or between the metabolite concentrations and voxel tissue composition [GM/(GM+WM)].

Conclusions This study suggests that TLE can produce metabolic changes to DLPFC that is remote from the seizure focus.

Key Points

- *Magnetic resonance spectroscopy probes the brain metabolism noninvasively.*
- *Dorsolateral prefrontal reductions in NAA (a neuronal marker) and Ins are observed in TLE.*
- *Temporal lobe epilepsy can result in metabolic changes remote from the seizure focus.*

Keywords Magnetic resonance spectroscopy · Temporal lobe epilepsy · Dorsolateral prefrontal cortex · Brain · Metabolism

Abbreviations

1H-MRS	Proton magnetic resonance spectroscopy	CHES	Chemical shift selective
ANOVA	One-way analysis of variance	Cho	Choline, including glycerophosphocholine and phosphocholine
ANTs	Advanced normalization tools	contra	Contralateral to the epileptic focus

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Cr	Creatine + phosphocreatine
CSF	Cerebrospinal fluid
DLPFC	Dorsolateral prefrontal cortex
GM	Gray matter
Glx	Glutamate + glutamine
Ins	Myoinositol
ipsi	Ipsilateral to the epileptic focus
L+R	Average value of the left and right DLPFCs
L_sub_TLE	Left TLE subgroup
L	Left
LCModel	Linear combination model
LSD	Least significant difference
MPRAGE	Magnetization prepared rapid gradient echo
NAA	N-acetyl aspartate
PRESS	Point-resolved spectroscopy
R_sub_TLE	Right TLE subgroup
R	Right
TLE	Temporal lobe epilepsy
VOIs	Volumes of interest
WM	White matter

Introduction

Magnetic resonance spectroscopy (MRS) can provide in vivo biochemical information noninvasively. It has been used to investigate metabolic changes of many neurologic and neurosurgical disorders, such as in brain tumor, epilepsy, radiation injury, etc. [1]. MRS has been applied to investigate neuropathologic changes of temporal lobe epilepsy (TLE) noninvasively by detecting and quantifying endogenous metabolites including *N*-acetyl aspartate (NAA, a marker for neuronal status and integrity), choline (Cho, a marker for membrane integrity and turnover), creatine (Cr, a marker for energy metabolism), myoinositol (Ins, a marker for glial cell integrity), and glutamate + glutamine (Glx, related to excitatory neurotransmission) [2]. The most common finding is the reduction of NAA in the temporal/hippocampal regions. Other findings include decreases in NAA/Cr, NAA/Cho, and NAA/(Cr+Cho). Together, these findings are thought to reflect neuronal dysfunction or neuronal loss and reactive gliosis of astrocytes [3–6]. However, most previous spectroscopic studies were focused on the metabolic changes of the hippocampi and/or temporal lobe, and little attention has been paid to frontal brain regions more remote from common seizure foci.

The frontal lobe is remarkable for its rich interconnectivity with other brain regions, and ictal and/or interictal epileptiform discharges arising from the temporal lobe may spread to this area [7]. High-level cognitive functions supported by the frontal lobe have been shown to be compromised in TLE patients [8, 9]. As a key functional part of the frontal lobe, the dorsolateral prefrontal cortex (DLPFC) plays an important role in functions such as working memory, planning, emotions, etc. [10]. Its

functional organization is a matter of study in different fields of medicine. So, in this study, we intend to use single-voxel spectroscopy (SVS) to investigate possible metabolic changes that may occur in the DLPFC of TLE patients.

Since metabolite ratios such as NAA/Cr and NAA/(Cr+Cho) provided mixed information of more than one metabolite, we quantified metabolite concentrations (relative to internal water signal) to facilitate the unambiguous interpretation of each metabolite. We also performed tissue segmentation and cerebrospinal fluid (CSF) correction based on high-resolution T1-weighted images to eliminate the contamination of CSF and resulting underestimation of the metabolite concentrations.

Materials and methods

Participants

Twenty-four MRI-negative TLE patients (10 males and 14 females; age range 16–46 years; mean age 27.8 years) and 22 normal controls (8 males, 14 females; age range 22–61 years; mean age 29.0 years) were studied (Table 1). Diagnosis of TLE was based on clinical history, seizure description, and long-term video electroencephalography findings. Patients were divided into two subgroups (the left TLE subgroup, $n = 14$, and right TLE subgroup, $n = 10$) according to the localization of their seizure foci. That is, the right TLE subgroup included those patients whose seizure foci were in the right temporal lobe, and vice-versa. All studied participants were right-handed.

MRI and MRS acquisition

MR scans were performed on a Siemens Tim Trio 3-T scanner (Siemens Healthcare, Erlangen, Germany) with an eight-channel phased array head coil. Initial image acquisition included a high-resolution T1-weighted scan that acquired with Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequence (TR/TE = 2250/2.6 ms, flip angle 9°, 192 sagittal slices of 1 mm thickness were collected, with a matrix size of 256 × 256 over a FOV of 256 × 256 mm). Axial and coronal images were reconstructed based on the sagittal images to enable a three-dimensional view of the volumes of interest (VOIs) during MRS localization.

Single-voxel ¹H-MRS acquisitions were performed using a point-resolved spectroscopy (PRESS) sequence with the following parameters: TR/TE = 2000/30 ms; number of averages = 128; bandwidth = 1200 Hz. VOIs were positioned bilaterally in the DLPFC (Fig. 1). The voxels were carefully placed to include the most gray matter and least white matter, with a fix size of 20 × 40 × 15 mm. Spectra with and without water suppression were both acquired. The water suppression was achieved by three chemical shift-selective (CHESS) pulses prior to the PRESS module. The total scan time was approximately 16 min.

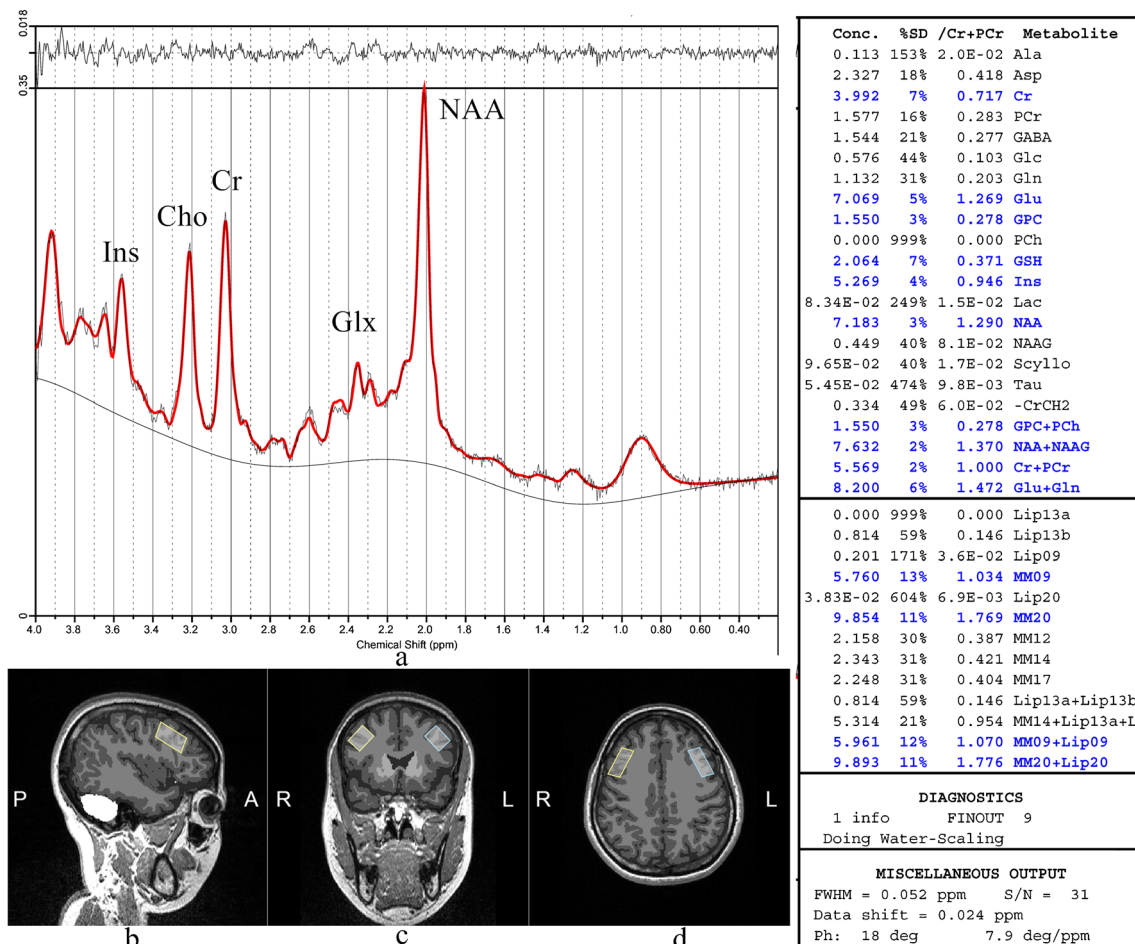


Fig. 1 Quantification of the metabolites. Concentration of metabolites was first estimated by the LCModel (a) and then corrected for cerebrospinal fluid contamination. The voxel CSF volume fraction was determined by overlaying the voxel on the segmented T1-weighted images (b, c, d)

All studied participants were free of significant clinical findings by MRI. If there were any uncertainties, more sequences (such as T2, T2_FLAIR) would be done to make sure that all studied participants were MRI negative.

MR data postprocessing

Raw spectral data were exported and processed with the Linear Combination Model (LCModel, version 6.3-1H, Provencher SW, <http://s-provencher.com/lcmodel.shtml>), a widely used software tool for automatic quantification of in vivo proton MR spectra without parameter tuning. It analyzes the in vivo spectrum as a linear combination of a basis set of complete model spectra of in vitro metabolite solutions. Complete model spectra, rather than individual resonances, are used to incorporate maximum prior information into the analysis. A model-free constrained regularization method automatically accounts for differences in phase, baseline, and line shapes between the in vitro and in vivo spectra and estimates the metabolite concentrations and their uncertainties [11, 12]. No

additional spectral apodization or zero-filling was performed prior to LCModel analysis. Spectra with and without water suppression were both acquired. Concentrations of brain metabolites were quantified by the LCModel using the tissue water signal as an internal reference. Metabolite levels were reported in institutional units. Only those spectra with a signal-to-noise ratio (SNR) ≥ 15 , full-width at half-maximum (FWHM) ≤ 0.08 ppm, and Cramer-Rao lower bounds (CRLB) $< 15\%$ were included for analysis.

To correct for the contamination of cerebrospinal fluid (CSF) contained in the SVS voxels, each subject's T1-weighted images were segmented into gray matter (GM), white matter (WM), and CSF using the cortical thickness procedure of Advanced Normalization Tools (ANTs, 10.1016/j.neuroimage.2014.05.044). The voxel CSF volume fraction was determined by overlaying the voxel on the segmented T1-weighted images (Fig. 1). Finally, metabolite concentrations (corrected for CSF volume) were calculated as follows [13–15]:

$$C_{cor} = C_{raw} \times [V_{total} / (V_{total} - V_{CSF})]$$

where C_{cor} is the corrected value, C_{raw} is the uncorrected value, and V_{total} and V_{CSF} represent the total volume of the voxel and the volume of CSF within the voxel, respectively.

Statistics

Group differences in age were assessed by an independent sample *t*-test, and the gender distribution was examined using a chi-square test. Normality of distribution of the data was tested with the Shapiro-Wilk test. Analyses of MRS data were focused on metabolic asymmetry in the controls, metabolite differences in TLE patients, and whether metabolite reductions were lateralized to the same side as the seizure foci. First, paired *t*-tests were applied in the controls and the patients to identify possible metabolic asymmetry between the left DLPFC and the right DLPFC. In the patient group, seven patients' data were excluded because of an insufficient signal-to-noise ratio for either the left or the right side. Second, metabolite concentrations of the patients in DLPFCs ipsilateral and contralateral to the seizure foci were compared with the pooled values (average of the left DLPFC and right DLPFC) of the controls using one-way analysis of variance (ANOVA). Least significant difference (LSD) post hoc testing was performed. Third, comparisons between the TLE subgroups and controls at the same side (e.g., the left DLPFC of the left TLE subgroup vs. the left DLPFC of the controls) were performed using an independent sample *t*-test. Finally, correlation analyses were performed between the metabolite concentrations and epilepsy duration and between the metabolite concentrations and voxel tissue composition [GM/(GM+WM)]. $p < 0.05$ was considered statistically significant.

Results

There were no significant differences between the patients and controls in age and gender distribution. Metabolite concentrations are summarized in Table 2. The average quality indexes for MRS data were as follows: SNR = 26, FWHM = 0.05 ppm, CRLB of NAA = $3.2 \pm 0.8\%$, Ins = $4.4 \pm 1.1\%$, Cr = $2.2 \pm 0.5\%$, Cho = $3.0 \pm 0.7\%$, and Glx = $5.4 \pm 1.2\%$. Differences that reached significant level are marked in Table 1 as well as in Figs. 2–5.

In healthy controls, the NAA concentration of the left DLPFC was statistically higher than that of the right ($p = 0.017$). However, such asymmetry was not seen in TLE patients ($p > 0.05$) (Table 2, Fig. 2). No significant difference was found in other metabolites between the left and right DLPFCs in either healthy controls or TLE patients.

Compared with the pooled values of the controls, the patients' NAA concentrations showed a significant reduction in the DLPFC, both ipsilateral to the epileptic focus ($p = 0.018$) and contralateral to the epileptic focus ($p = 0.048$) (Table 2,

Table 1 Clinical and demographic data

	TLE patients ($n = 24$)	Controls ($n = 22$)
Gender (male/female)	10/14	8/14
Age (years)	27.75 ± 8.03 (16–46)	29.00 ± 9.38 (22–61)
Handedness (right/left)	24/0	22/0
Duration (years)	9 ± 6.7 (0.2–27)	-

Fig. 3). The Ins of the patients was also decreased compared with that of the controls (ipsilateral: $p = 0.060$; contralateral: $p = 0.014$) (Table 2, Fig. 3).

Compared with the same sides of the controls, the left DLPFC of the left TLE subgroup showed significantly decreased NAA ($p = 0.003$) and Ins ($p = 0.043$) (Table 2, Fig. 4), and the left DLPFC of the right TLE subgroup also demonstrated marked reduction of NAA ($p = 0.002$) and Ins ($p = 0.012$) (Table 2, Fig. 5). Metabolites of the right DLPFCs in both subgroups did not demonstrate any significant changes.

Correlations between the metabolite concentrations and epilepsy duration and between the metabolite concentrations and voxel tissue composition [GM/(GM+WM)] did not reach significance (Tables 3 and 4).

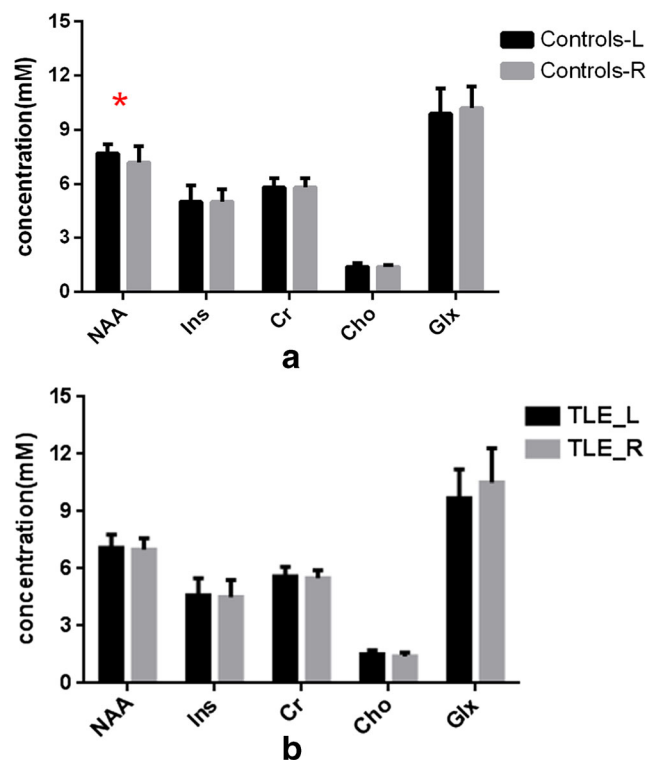


Fig. 2 Metabolic difference between the left and right DLPFC in the controls as well as patients. Comparisons between the left and right DLPFC in the controls (a) showed that the NAA concentration of the left DLPFC was significantly higher than that of the right. However, such metabolic asymmetry disappeared in the patients (b). $*p < 0.05$

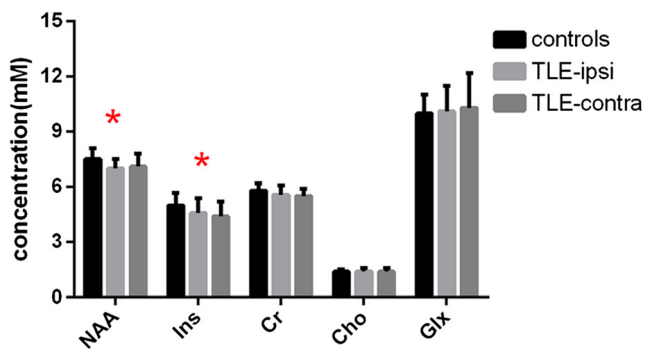


Fig. 3 Metabolic difference: the patients vs. the controls in the ipsilateral and contralateral DLPFC. Compared with the pooled values of the controls, TLE patients showed a significant decrease of NAA in both the ipsilateral and contralateral DLPFC; Ins of the contralateral DLPFC also significantly decreased. There were no significant differences between the ipsilateral and contralateral DLPFC metabolites. * $p < 0.05$

Discussion

Several findings were identified in this study: (1) metabolite levels in the right and left DLPFCs were not identical in controls, with the NAA concentration of the left DLPFC significantly higher than that of the right. (2) Compared with controls, TLE patients showed significantly decreased NAA and Ins, with larger reductions on the left. (3) No correlation was found between the metabolite concentrations and the epilepsy

duration or between the metabolite concentrations and voxel tissue composition [GM/(GM+WM)].

NAA is synthesized in brain mitochondria and almost exclusively concentrated in neurons. Reduction of NAA is generally interpreted in terms of dysfunctional mitochondrial metabolism or loss of neurons [16]. In this study, we found that the NAA concentration of the left DLPFC was statistically higher than that of the right in the controls. In fact, biochemical asymmetry has been reported in previous studies [17–19]. For example, Jayasundar [19] studied 168 volunteers and found that there were significant differences between metabolite ratios of the left and right hemisphere, among which NAA/Cr was much higher in the left frontal lobe than in the right frontal lobe. Metabolic asymmetry was believed to be related to the anatomical asymmetry between the two hemispheres. Studies have shown that there is more gray matter relative to white matter in the left hemisphere than the right, particularly in the frontal and precentral regions [20–22]. Specifically, Amunts et al. [21] found that the left central sulcus was deeper than the right central sulcus in righthanders, and this anatomical asymmetry was complemented by a left-larger-than-right asymmetry in neuropil volume in Brodmann’s area 4. In our study, all participants were righthanded. Therefore, we speculate that the observed NAA asymmetry in normal controls may reflect the anatomy asymmetry between the dominant and non-dominant hemisphere.

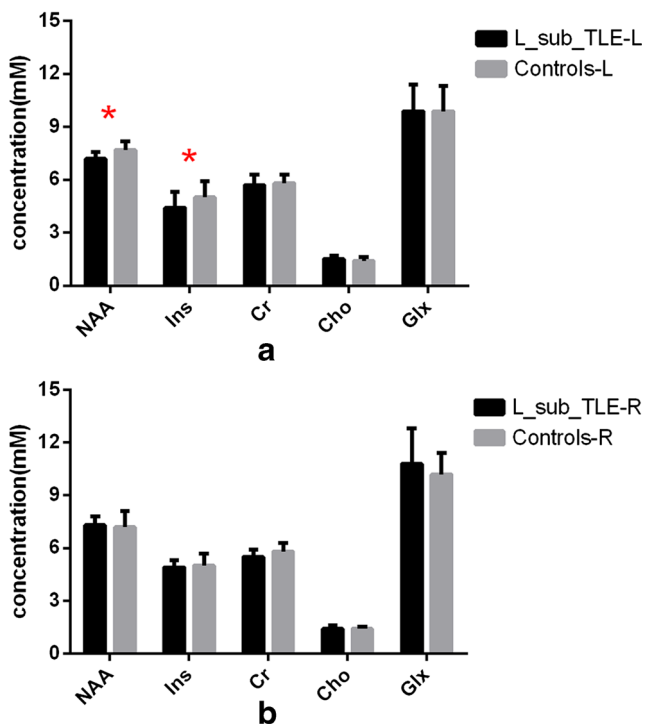


Fig. 4 Metabolic difference: the left TLE subgroup vs. the controls in the left and right DLPFCs. Compared with controls, TLE patients of the left subgroup showed a significant decrease of NAA and Ins in the left DLPFC (a). No significant changes were found in the right DLPFC (b). * $p < 0.05$

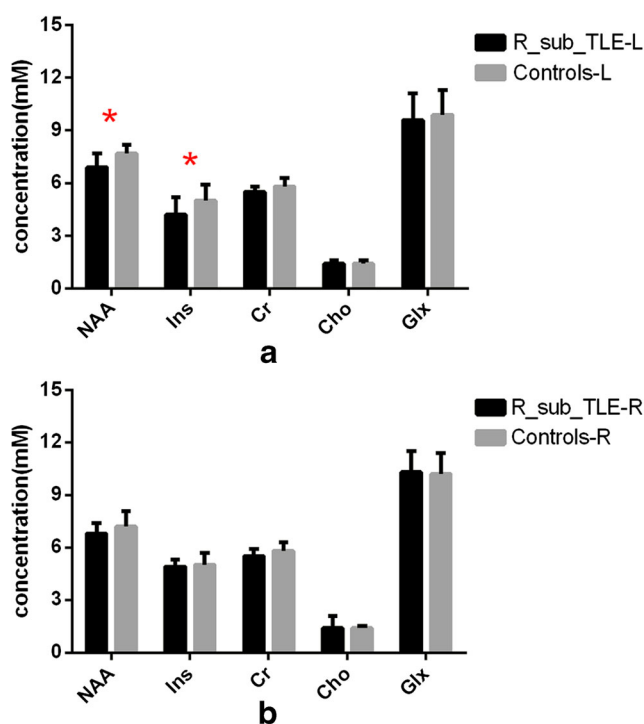


Fig. 5 Metabolic difference: the right TLE subgroup vs. the controls in the left and right DLPFCs. Compared with controls, TLE patients of the right subgroup also demonstrated a significant decrease of NAA and Ins in the left DLPFC (a). No significant changes were found in the right DLPFC either. * $p < 0.05$

Table 2 Metabolite concentrations (mmol/kg wet weight) of DLPFC in TLE patients and healthy controls

	Controls-L (22)	Controls-R (22)	Controls-L+R (22)	TLE-L (17)	TLE-R (17)	TLE-ipsi (22)	TLE- contra (19)	L_sub_ TLE-L (14)	L_sub_ TLE-R (11)	R_sub_ TLE-L (8)	R_sub_ TLE-R (8)
NAA	7.7 ± 0.5	7.2 ± 0.9^a	7.5 ± 0.6	7.1 ± 0.7	7.0 ± 0.6	7.0 ± 0.5^b	7.1 ± 0.7^b	7.2 ± 0.4^c	7.3 ± 0.5	6.9 ± 0.8^c	6.8 ± 0.6
Ins	5.0 ± 0.9	5.0 ± 0.7	5.0 ± 0.7	4.6 ± 0.9	4.5 ± 0.9	4.6 ± 0.8	4.4 ± 0.8	4.4 ± 0.9^c	4.9 ± 0.4	4.2 ± 1.0^c	4.9 ± 0.4
Cr	5.8 ± 0.5	5.8 ± 0.5	5.8 ± 0.4	5.6 ± 0.5	5.5 ± 0.4	5.6 ± 0.5	5.8 ± 0.5	5.7 ± 0.6	5.5 ± 0.4	5.5 ± 0.3	5.5 ± 0.4
Cho	1.4 ± 0.2	1.4 ± 0.1	1.4 ± 0.1	1.5 ± 0.2	1.4 ± 0.2	1.4 ± 0.2	1.4 ± 0.2	1.5 ± 0.2	1.4 ± 0.2	1.4 ± 0.2	1.4 ± 0.7
Glx	9.9 ± 1.4	10.2 ± 1.2	10.1 ± 1.0	9.7 ± 1.5	10.5 ± 1.8	10.1 ± 1.4	10.3 ± 1.9	9.9 ± 1.5	10.8 ± 2.0	9.6 ± 1.5	10.3 ± 1.2

Bold entries with a superscript 'a', 'b' or 'c' indicate statistical significance: ^a $p < 0.05$ compared with the left DLPFC of the normal controls; ^b $p < 0.05$ compared with the pooled values of the left and right (L+R) DLPFCs; ^c $p < 0.05$ compared with the left DLPFC of the healthy controls

Another finding of this study was that concentrations of NAA in DLPFC, either ipsilateral or contralateral to the seizure focus, were significantly decreased compared with the controls. Spectroscopic abnormalities outside the seizure focus have been consistently reported in recent years [23–27]. For example, using 3D spectroscopic imaging techniques, Mueller et al. [25] found a widespread, bilateral NAA/(Cr+Cho) reduction extending beyond the temporal region in TLE patients. Metabolic changes outside seizure foci may be related to the propagation of seizure activity. When a patient is having a seizure, it is common to see that epileptiform discharges originated from the temporal lobe spread to other brain regions, like the frontal lobe [7], perhaps inducing metabolic changes accordingly.

It was interesting that NAA reductions were greater in the left DLPFC (when compared with the same side of the controls), even when the seizure focus was on the right side (i.e., the right TLE subgroup). The reason for this is unclear. The most common pathway of seizure propagation in temporal lobe epilepsy is from the initiating temporal lobe to the ipsilateral frontal lobe, then to the contralateral frontal lobe, and finally to the contralateral temporal lobe [7]. However, studies have also shown that seizure activity may spread to the contralateral lobe directly, i.e., from the initiating the temporal lobe to the contralateral temporal lobe and then to the contralateral frontal lobe [7]. In our study, metabolic changes were

found to be more prominent in the left DLPFC, even when the seizure focus was on the right temporal lobe.

Observed changes in Ins were similar to those in NAA: it was lower in patients than controls, and reductions were greater on the left. Ins is considered as a biomarker of glial cell integrity. Increased Ins is usually seen in lesions with gliosis, such as glioma. Gliosis is usually visible on MRI, whereas all the participants in our study were negative on MRI. On the other hand, Ins has a well-accepted function in intracellular signal transduction and plays an important role in cellular osmoregulation [28]. Studies in animals have shown that hyposmolality caused by osmotic dysregulation could be compensated by rapid Ins reduction [29]. Low Ins levels have been reported in previous MRS studies [23, 30] of epilepsy, and Wellard et al. [23] interpreted reduced Ins as reflecting osmotic dysregulation after seizure activity.

Cr is reported to be relatively constant and unaffected by the presence of pathology, so it is often used as an internal reference for calculating metabolite levels [31]. Our findings of non-significant changes of Cr supported this viewpoint. Cho is a constituent of the membrane. High Cho concentrations indicate damage to the membrane integrity or an increase in membrane turnover. Increased Cho was not observed in this study, indicating that the neuron structure still remained intact. Glx is the sum of glutamine and glutamate. Increased glutamate levels have been shown to be implicated in the pathophysiology of epilepsy by both in-vivo [32, 33] and ex-vivo

Table 3 Correlation between metabolite concentrations and epilepsy duration

	Ipsilateral		Contralateral	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
NAA	-0.195	0.385	0.143	0.559
Ins	0.331	0.159	0.444	0.057
Glx	0.112	0.621	-0.143	0.558
Cr	0.035	0.877	0.429	0.067
Cho	0.245	0.271	0.202	0.408

Table 4 Correlation between metabolite concentrations and voxel tissue composition [GM/(GM+WM)]

	Ipsilateral		Contralateral	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
NAA	0.137	0.544	0.148	0.545
Ins	0.393	0.070	0.355	0.136
Glx	0.156	0.489	0.610	0.066
Cr	0.404	0.062	0.480	0.088
Cho	-0.130	0.565	-0.179	0.464

[32, 34] studies. Elevated Glx has also been reported in TLE and is thought to reflect the hyperexcitability of the seizure focus [15]. However, no significant change in Glx was identified in the current study, indicating that the spectroscopic abnormalities of the frontal lobe were secondary to the seizure propagation that originated from the temporal lobe.

The present study has several limitations: First, the study population was small, which may reduce the statistical power. If a study with a larger population and corrections for multiple comparisons could verify our findings, the results would be more convincing. Second, we did not acquire the temporal lobe data because of the acquisition time limitation, so we were not able to investigate the changes of the temporal lobe at the same time. Third, patients were not asked to stop their antiepileptic drugs (AEDs) before examination because of ethical considerations. However, according to previous studies, AEDs can help to recover NAA and prevent neuronal and axonal damage/dysfunction [35, 36], so we believe that the NAA and Ins reduction in our study were not caused by AEDs.

In conclusion, the current study demonstrates that metabolic impairments in TLE are not restricted to the temporal lobe. TLE affects brain regions far beyond the seizure focus, such as the DLPFC, and causes metabolic changes accordingly. But the changes are not equal between the left and the right sides, i.e., the left DLPFC is more susceptible to such impairment. Such unequal changes lead to the disappearance of the metabolic asymmetry observed in healthy controls. A study with a larger population should seek to replicate these findings, and further mechanistic studies are warranted.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Dr. Yue.

Conflict of interest The authors of this manuscript declare no relationships with any companies.

Statistics and biometry No complex statistical methods were necessary for this paper.

Ethical approval Institutional Review Board approval was obtained.

Informed consent Written informed consent was obtained from all patients in this study.

Methodology

- prospective
- cross-sectional study
- performed at one institution

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