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REVIEW

Usefulness of magnetic resonance spectroscopy in mesial temporal sclerosis: a systematic review

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Abstract

Background Magnetic resonance spectroscopy (MRS) provides non-invasive information about metabolic features in different regions of the brain affected by mesial temporal sclerosis (MTS).

Purpose To review articles analyzing the most common alterations in biochemical parameters in MTS and the applications of MRS in presurgical assessment.

Methods We undertook a systematic literature search for MRS in MTS in PubMed, SCOPUS, and Cochrane based on the MESH terms ""Magnetic Resonance Spectroscopy", "Proton Magnetic Resonance Spectroscopy", "Carbon-13 Magnetic Resonance Spectroscopy", "1H-MRS", "31P-MRS", "mesial temporal sclerosis", "hippocampal sclerosis", "mesial temporal seizure", and "mesial temporal epilepsy".

Results Of the initial 134 articles found, 30 were selected after the exclusion process. Of these, 13 detected a decrease in N-acetylaspartate (NAA), 9 showed a decreased in the ratio NAA/Cho+Cr, and 8 demonstrated a decreased in the ratio NAA/Cr, all of them in the ipsilateral hippocampus. Nine studies also found reduced NAA levels in extrahippocampal regions.

Conclusions The main findings were a decrease in NAA in the ipsilateral hippocampus. In addition, NAA levels were low outside the hippocampus so MTS could be a more extensive disease. Patients without MTS also presented a decrease in NAA in the ipsilateral hippocampus although NAA was even lower in the MTS patients. Thus, MRS could be useful in the presurgical evaluation to locate the epileptogenic focus, but not specific for the diagnosis of MTS.

Keywords Mesial temporal sclerosis · Hippocampal sclerosis · Magnetic resonance spectroscopy · 1H-MRS · 31P-MRS · N-acetylaspartate

Abbreviations

Cr	Creatine
Cho	Choline
Glx	Glutamine
MRS	Magnetic resonance spectroscopy
MTS	Mesial temporal sclerosis
NAA	N-acetylaspartate
n-MTS	No signs of mesial sclerosis
1H-MRS	Proton magnetic resonance spectroscopy
mI	Myo-inositol
31 P-RM-e	Phosphorus magnetic resonance spectroscopy
PCr	Phosphocreatine
PDE	Phosphodiesters
PME	Phosphomonoesters.

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Introduction

About a quarter of patients with epilepsy fail to respond to medical treatment, experiencing an increase in morbidity and mortality compared to the general population [1]. One of the

most common forms of epilepsy associated with a poorer response to antiepileptic drugs is temporal lobe epilepsy with mesial sclerosis (MTS).

In most cases of MTS, surgical treatment reduces, either in whole or in part, the frequency of epileptic seizures, improving the quality of life of drug-resistant patients. In addition, resective surgery plus antiepileptic drugs results in a lower probability of seizures than antiepileptic treatment alone [2–4].

Hippocampal resection is the most frequent surgical procedure in MTS. However, it requires an exhaustive presurgical evaluation to select patients who could benefit from surgery; reduce the morbidity and mortality associated with the procedure, although this is below 1% [5]; and identify the epileptogenic focus of seizures. Different non-invasive techniques have been developed to help with this assessment, providing structural and functional information about the epileptogenic focus. One such technique is magnetic resonance spectroscopy (MRS).

Magnetic resonance spectroscopy

Magnetic resonance spectroscopy is a non-invasive technique able to evaluate the products of metabolism in a living tissue, detecting possible dysfunctions and supplementing the information provided by MR. To do this, it is necessary to choose a spectrum and the region to study. The different spectra in MRS include.

Proton magnetic resonance spectroscopy (1H-MRS)

This is the most used MRS modality due to the abundance of hydrogen in the tissues of the human body. The metabolites studied in 1H-MRS include [6–9] (1) N-acetylaspartate (NAA), considered to be a marker of neuronal function as it is a product of the oxidative metabolism of neuronal mitochondria, and NAA has an osmoregulatory function and is absent in glial cells; (2) creatine (Cr) and choline (Cho), which are present in neurons and, in higher concentrations, in astrocytes, and Cr and Cho are related to intracellular bioenergetic functions; (3) Myo-inositol (mI), associated with osmoregulation and intracellular signaling; and (4) Glutamate+Glutamine (Glx), the most important excitatory neurotransmitters in the neuronal synapse. Furthermore, *NAA/(Cho+Cr)*, *NAA/Cr*, *NAA/Cho*, and *Cr/NAA* are used in the evaluation of bioenergetic and neuronal functions.

Phosphorus magnetic resonance spectroscopy (31 P-RM-e) [7, 10]

This allows the measurement of phosphorus metabolites related to the energy state and membrane composition of human brain cells. This includes products of membrane synthesis such as phosphodiesters (PDE) or phosphomonoesters (PME). ATP (α, β, γ), phosphocreatine (PCr), and inorganic phosphate reflect the energy demand of the brain region studied.

Other spectra that can be used in MRS are 13C, 7Li, and 19F. However, they are only available in a few specialized research centers.

Single voxel and multiple voxel magnetic resonance spectroscopy

Once we have chosen the spectrum we then select a brain region to study [7, 9].

Single voxel magnetic resonance spectroscopy

This consists of selecting a unique voxel, which can acquire multiple shapes. The voxel must be placed in regions, which are not affected by air or water interphases. Single voxel is especially indicated in brain diseases in which imaging abnormalities are shown on MR, such as MTS.

Multiple voxel magnetic resonance spectroscopy

This allows spectroscopic data from several voxels to be obtained at the same time. It is commonly used in diseases without MR abnormalities, such as temporal epilepsy with no signs of mesial sclerosis (n-MTS)

The purpose of our systematic review was to collect the main findings obtained by MRS in MTS patients and to determine its usefulness in presurgical evaluation.

Materials and methods

A systematic literature search for MRS in MTS was made in the databases PubMed, SCOPUS, and The Cochrane Library Plus, based on the MESH terms ""Magnetic Resonance Spectroscopy", "Proton Magnetic Resonance Spectroscopy", "Carbon-13 Magnetic Resonance Spectroscopy", "1H-MRS", "31P-MRS", "mesial temporal sclerosis", "hippocampal sclerosis", "mesial temporal seizure", "mesial temporal epilepsy", and the Boolean operators (AND, OR). We did not use additional filters. After removing 23 duplicates, there were 134 articles. We chose articles according to the PRISMA scale [11] (Preferred Reporting Items for Systematic Reviews and Meta-analyses), which is composed of phases summarized in Fig. 1.

First, we performed a critical reading of titles and abstracts. Our inclusion criteria were articles in which patients with MTS were evaluated with MRS in its different modalities. In addition, we included publications in which MRS was correlated with other tests (Video-EEG, neuropsychological tests, volumetry, or histopathology).

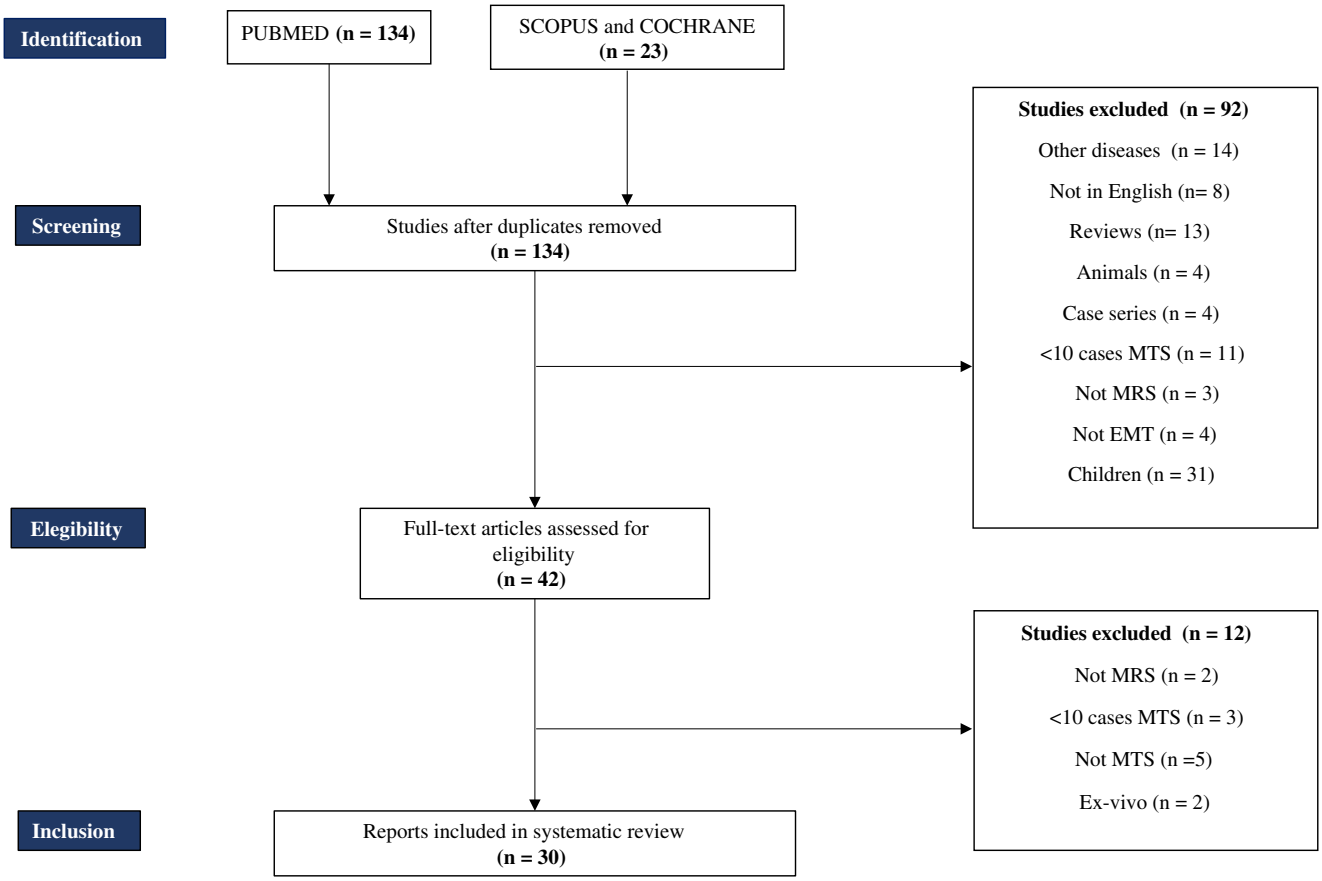

Fig. 1 Search strategy flowchart

Our exclusion criteria were (1) studies of other epilepsies, (2) studies which only included temporal epilepsy without sclerosis (n-MTS), (3) articles without an English version, (4) reviews, (5) animal studies, (6) case series, (7) studies with fewer than 10 patients with MTS, and (8) studies involving children.

After screening by title and abstract, we read the full text of the remaining 42 articles. Five articles were rejected because it was not specified that the temporal epilepsy was due to sclerosis. Three articles were excluded because there were fewer than ten cases of MTS. Two articles in which no MRS was performed and two articles in which spectroscopic evaluation was made on resected brain tissue were also excluded. Thus, 30 studies were finally included in our systematic review.

Results and discussion

We undertook a systematic review of articles reporting the spectroscopic data obtained from patients with MTS in order to examine the application of MRS in presurgical evaluation. The review finally included 30 studies, summarized in Table 1, which specifies author and year of publication, objectives, design, brain region studied, MRS characteristics, additional tests, and results. Of these 30, 23 included MRS as part of the presurgical evaluation of patients with MTS [10, 12–33], while 2 studies performed MRS after surgery [34, 35]. The remaining 5 did not specify whether MRS was included for presurgical or postsurgical assessment [36–40].

MRS studies in ipsilateral hippocampus

The main findings were found in the ipsilateral hippocampus, showing a decrease in NAA (13/30 studies) [12, 13, 15, 19, 21, 23–25, 28, 29, 31, 32, 38], a decrease in the ratio NAA/Cho+Cr (9/30 studies) [17, 18, 30, 33, 34, 36, 37, 39, 40], and a decrease in the ratio NAA/Cr (8/30 studies) [14, 16, 20, 22, 26, 27, 35, 39]. MTS was traditionally associated with a neuron loss in the hippocampus [23]. More recent studies hypothesized that there is a relationship between MTS and neuronal mitochondrial dysfunctions [41]. NAA is a product of the Krebs Cycle, which takes place in the mitochondria, so the alterations observed in these 29 articles seem to be consistent with the mitochondrial dysfunction theory. In addition, as NAA has a role in the osmoregulation of neurons [8], low NAA levels cannot maintain the integrity of these cells, resulting in neuron loss.

Table 1 Studies with Magnetic Resonance Spectroscopy in Mesial Temporal Sclerosis

Author/ year	Objectives	Design	Region	MRS	Additional test	Results
Park et al. [10] (2015)	Evaluation of extratemporal energetic changes	*N*=64 (*n*=33 MTS vs. *n*=31 c)	Ips and ctl AIBG, PIBG, FL	Multiple voxel 31-P MRS 3.0T (PDE, PME, Pi, PCr, tATP, γ-ATP, PCr/ATPt, PCr/γ-ATP, PCr/γ-ATP, PCr/Pi)		- Ips AIBG: ↓Pi (p=0,009), ↓PCr/ γ-ATP (p=0,027) - Ctl AIBG: ↓Pi (p=0,013) ↑ tATP (p=0,026) - Ips PIBG: ↓Pi (p=0,009), ↓PCr/ γ-ATP (p=0,017), ↑ γ-ATP (p=0,024) - Ctl frontal lobe: ↓Pi (p=0,014)
Mueller et al. [36] (2011)	Evaluation of extrahippocampal changes.	*N*=43 (*n*=12 MTS vs. *n*=13 n-MTS vs. *n*=18 c)	Ips and ctl temporal, frontal, occipital lobe	Multiple voxel 1H-MRS 1.5T (NAA, Cr, Cho, NAA/ (Cho + Cr)		-↓NAA/ (Cho+Cr) temporal, occipital and frontal lobes bilaterally in MTS -↓NAA/ (Cho+Cr) in n-MTS, mostly in bilat. temporal and frontal lobes.
Mantoan et al. [37] (2009)	Correlation with interictal discharges and memory	*N*=53 (*n*=29 MTS vs. *n*=24 c)	Ips and ctl AHIP	Single voxel 1H-MRS 1.5T NAA, Cr, Cho, NAA/ (Cho + Cr)	Video-EEG, IQ, WAIS-R, Logical Memory and I and II, Test Rey and-Osterrieth, RAVLT	-↓NAA/ (Cho+Cr) in ips hippocampus vs. ctl correlated with an increase in interictal discharges (p=0.006) - Left MTS: correlation between NAA/ (Cho + Cr), duration of epilepsy (p=0.027), and worse results in RAVLT. - Right MTS: correlation between NAA/(Cho+Cr) with worse results in IQ and logical memory and delayed recall
Doelken et al. [38] (2008)	Evaluation of spectroscopic differences	*N*=49 (*n*= 17 MTS vs. *n*=9 n-MTS vs. *n*=23 c)	Ips and ctl AHIP	Single voxel 1H-MRS 1.5T (tNAA, Glx, mI)		- ↓tNAA in MTS and n-MTS ($p < 0.001$).
Doelken et al. [12] (2007)	Correlation with EEG, SPECT, Engel.	*N*=49 (*n*= 25 MTS vs. *n*=24 n-MTS)	Ips and ctl hippocampus	Single voxel 1H-MRS 1.5T, tNAA, Cho, Cr, Glx, mI, NAA/(Cho+ Cr)	EEG, SPECT, Engel	- 82% MTS and 71% n-MTS with abnormalities presented spectroscopic changes in ips hippocampus. - 28% n-MTS and MTS presented ctl spectroscopic changes. -Unilat. and concordant findings of EEG, SPECT, MRS to the operated hemisphere had a better postoperative outcome (p= 0.08).
Fojtiková et al. [39] (2007)	Evaluation of thalamus	*N*=40 (*n*=20 MTS vs. *n*=20 c)	ips and ctl hippocampus	Single Voxel 1H-MRS 1.5T (NAA, NAA/Cr, NAA/ (Cho + Cr))	EEG	- ↓NAA in ips and ctl thalamus vs. c. (p=0.02) - ↓NAA, NAA/Cr and NAA/ (Cho + Cr) in ips thalamus vs. ctl (p<0.001) - ↓NAA in ips hippocampus and ctl vs. c. (p<0.001) - ↓NAA, NAA/Cr, NAA/ (Cho + Cr) in ips hippocampus vs. ctl (p=0.006)
Briellman et al. [13] (2007)	Evaluation of spectroscopic differences	*N*=101 (*n*= 24 refract MTS vs. *n*= 17 no refract MTS vs. *n*= 60 c)	Ips and ctl Hippocampus, amygdala, WM anterior temporal and frontal lobes	Single Voxel 1H-MRS 3.0T (NAA, Cho, Cr, mI, Glx).	T2-relaxation, volumetry.	- ↓ NAA in refract MTS vs. no refract MTS (p<0.05) - ↓Glx ips in refract MTS

Table 1 (continued)

Author/ year	Objectives	Design	Region	MRS	Additional test	Results
Imbesi et al. [14] (2006)	Correlation between size and position of voxel with epileptogenic foci	*N*=15 (*n*= 10 MTS vs. *n*= 5 c)	Ips and ctl hippocampus	Single voxel 1H-MRS 1.5T (NAA/Cr, Cho/Cr).		- Rectangular Voxel (1x2x4 cm): ↓NAA/Cr ips vs. ctl. in *n*=10 MTS - Cubic Voxel (2x2x2 cm) ↓NAA/Cr ips vs. ctl in *n*=6 MTS
Riederer et al. [15] (2006)	Evaluation of spectroscopic differences	*N*=43 (*n*=12 MTS vs. *n*= 9 n-MTS vs. *n*=22 c)	Ips and ctl temporal lobe	Single voxel 1H-MRS 3.0T (NAA, Cr, Cho, Glx, Glu, Gln, mI, mI/Cr)		- ↓NAA ips and ctl in MTS (p<0,001). - ↓mI in MTS (p=0,005) and n-MTS (p<0,001) vs. c. - ↓Cr in MTS vs. c (p=0,002). - ↓mI/Cr in n-MTS vs. MTS (p=0,004).
Lantz et al. [34] (2006)	Prediction MRS postoperative normalization	*N*=35 (*n*=12 MTS vs. *n*=3 n-MTS vs. *n*=20 c)	Ips and ctl temporal lobe	Multiple voxel 1H-MRS 1.5T (NAA, Cr, Cho, NAA/(Cho+Cr)		-↓NAA/(Cho+Cr) in ips hippocampus vs. ctl temporal lobe (p=0.000002) -Correlation between number of preoperative abnormal region and degree of postoperative normalization in ctl temporal lobe (p=0.02)
Lu et al. [40] (2006)	Evaluation of spectroscopic differences	*N*=83 (*n*=27 unilat MTS vs. *n*= 9 MTS bilat vs. *n*=31 n-MTS vs. *n*=16 c)	Ips and ctl hippocampus	Single voxel 1H-MRS 1.5T (NAA, Cr, Cho, NAA/(Cho+Cr)	EEG	- ↓NAA/(Cho+Cr) in ips hippocampus in unilat MTS (p<0.001) - ↓NAA/(Cho+Cr) in refract MTS (p=0.04) - NAA/(Cho+Cr) locates epileptogenic foci in *n*=49 of MTS and n-MTS
Lee et al. [16] (2005)	Evaluation of spectroscopic differences	*N*=104 (*n*=41 unilat MTS vs. *n*=43 neocortical epilepsy vs. *n*= 20 c)	Ips and ctl hippocampus	Single voxel 1H-MRS 1.5T (NAA, Cr, Cho, NAA/Cr, NAA/Cho)		- ↓NAA/Cr in ips hippocampus in MTS (p=0.01). - ↓NAA/Cho ips hippocampus in MTS (p<0.001) and neocortical epilepsy (p<0.05). - Correct localization of epileptogenic foci in 65.9% MTS. - NAA/Cho correlated with worse results after postsurgical treatment in MTS
Spencer et al. [35] (2005)	Postsurgical changes	*N*= 25 (*n*=4 MTS PSz vs. *n*=10 MTS SzF vs. *n*=11c)	Ips and ctl temporal lobe	Multiple voxel 1H-MRS 1.5T (N9AA, Cr, Cho, NAA/Cr		-↓NAA/Cr in MTS -↓NAA/Cr in ips and ctl temporal lobe in PSz group vs SzF groups (p=0.013).
Düzel et al. [17] (2003)	Correlation with volumetry of hippocampus	*N*=40 (*n*= 13 MTS vs. *n*= 9 n-MTS vs. *n*= 18 c)	Ips and ctl hippocampus	Single voxel 1H-MRS 1.5T (NAA, Cr, Cho, NAA/(Cho+Cr))	Volumetry diffusion MR	- Correlation between NAA/(Cho+Cr) and Diffusion Coefficient in MTS (p=0,001) - ↓NAA/(Cho+Cr), ↓ volumetry and ↑ Diffusion Coefficient in ips hippocampus in MTS vs. ctl.
Zubler et al. [18] (2003)	Spectroscopic changes in ctl temporal lobe	*N*= 50 (*n*=13 left MTS vs. *n*=16 right MTS vs. *n*=21 c)	Ips and ctl temporal lobe	Single voxel 1H-MRS 1.5T NAA, Cr, Cho, NAA/(Cho+Cr)		- ↓NAA/(Cho+Cr) in ips hippocampus (p < 0.0001). - ↓NAA/(Cho+Cr) ips temporal neocortex (p < 0.0001) - Right MTS presented ↓NAA/ (Cho + Cr) in ctl hippocampus (p = 0.0018).
Mueller et al.	Utility of mI	*N*= 48 (*n*=24 MTS vs. *n*= 8 n-MTS vs. *n*=16 c)	Ips and ctl AHIP and PHIP	Multiple voxel 1H-MRS 1.5T (NAA, Cr, Cho, mI)		

Table 1 (continued)

Author/ year	Objectives	Design	Region	MRS	Additional test	Results
[19] (2003)						- Correct localization of epileptogenic foci in AHIP in 82 % MTS and in 80 % n-MTS. -↓NAA in ips hippocampus vs. ctl (p = 0.03) and c (p = 0.012). -↓mI ips AHIP in MTS vs. c.
Park et al. [20] (2002)	Correlation with interictal discharges	N= 34 (n=18 unilat. refract. MTS vs. n=16 bilat refract MTS)	Ips and ctl temporal lobe	Single voxel 1H-MRS 1.5T (NAA, Cr, NAA/Cr), EEG	EEG	- NAA/Cr correlated with interictal discharges in ctl frontal lobe (p=0.027). -↓NAA/Cr in ips temporal lobe (p<0.05)
Capizzano et al. [21] (2002)	Evaluation of extrahippocampal changes.	N=27 (n=15 MTS vs. n=12 c)	Ips and ctl hippocampus, temporal operculum, insula, cerebellum, frontal, parietal, and occipital lobe	Multiple voxel 1H-MRS 1.5T (NAA, Cr, Cho, NAA/(Cho+Cr). AF |NAA| and NAA/(Cho+Cr).		-↓|NAA| in ips hippocampus vs. ctl (p<0.01) vs. c (p<0.001)). -↓|NAA| In ips temporal operculum, insula, and cerebellum (p<0.00001) vs. c (p<0.0001). - AF|NAA| in ips hippocampus located foci in 60% MTS. - Extrahippocampal AF|NAA| concordant with epileptogenic foci in EEG with 87% of sensitivity and 92% specificity (p<0.01).
Simister et al. [22] (2002)	Evaluation of spectroscopic differences	N=30 (n=10 MTS vs. n= 10 n-MTS vs. n=10 c)	Ips and ctl AHIP, MHIP, PHIP	Multiple voxel 1H-MRS 1.5T (NAA, tNAA, Cr, Cho, Glx, mI)		-↓tNAA in ips hippocampus in n=9 MTS. -↓tNAA, tNAA/Cr and tNAA/ (Cho+Cr) in ips AHIP in MTS. -↓tNAA in ips MHIP in n= 4 n-MTS. -↑Glx in ctl AHIP in n= 10 n-MTS.
Kuzniecky et al. [23] (2001)	Correlation with histopathology	N=60 (n=40 EMT vs. n=20 c)	ips y ctl temporal lobe	Multiple voxel 1H-MRS 4.1T (Cr/NAA)	Histopathology	- ↑Cr/NAA in ips hippocampus
Sawrie et al. [24] (2001)	Correlation with volumetry and verbal memory	N=22 (n= 6 right MTS vs. n=16 left MTS)	Ips and ctl hippocampus	Multiple voxel 1H-MRS 4.1T (Cr/NAA)	Volumetry, LM% (WMS)	- Volumetry of left hippocampus correlated with left Cr/NAA (p<0.01) - Volumetry of right hippocampus correlated with right Cr/NAA (p<0.05) - LM% correlated with left Cr/NAA (p<0.01)
Chang et al. [25] (2000)	Lateralization of epileptogenic foci	N=45 (n=25 MTS vs. n=20 c)	Ips and ctl hippocampus	Single voxel 1H-MRS 1.5T (NAA/Cho, NAA/Cr)		-↓NAA/Cr and NAA/Cho in ips hippocampus of MTS vs. hippocampus ctl vs. c (p<0.05). - Localization of affected hippocampus with MRS in 72% MTS - Localization of affected hippocampus 64% using voxel 6 cm^3 vs. 82% using voxel 2.25 cm^3
Feichtinger et al. [26]	Correlation between presurgical MRS	N=33 (n=12 MTS with ictal fear vs. n= 21 MTS without ictal fear)	Ips and ctl AHIP, MHIP, PHIP	Multiple voxel 1H-MRS 1.5T (NAA, Cho, NAA/Cho, and CSI score).		-↓NAA/Cho in AHIP (p<0.04) and MHIP (p<0.005) in MTS with ictal fear vs. MTS without ictal fear.

Table 1 (continued)

Author/ year	Objectives	Design	Region	MRS	Additional test	Results
(2001)	and ictal fear after surgery					Correlation between presurgical MRS and ictal fear after surgery
Meiners et al. [27] (2000)	Spectroscopic changes of temporal lobe white matter	*N*=23 (*n*=11 MTS vs. *n*=12 c)	Ips and ctl. temporal lobe white matter	Single voxel 1H-MRS 1.5T (NAA, Cr, Cho, NAA/Cr, NAA/Cho)		-↓NAA/Cho ips in temporal lobe white matter vs. ctl (p<0.01) vs. c (p<0.001). -↓NAA/Cr ips in temporal lobe white matter vs. ctl (p<0.05) vs. c (p<0.001)
Sawrie et al. [28] (2000)	Correlation with BNT	*N*=46 (*n*=32 left MTS vs. *n*=14 right MTS)	Ips and ctl hippocampus	Single voxel 1H-MRS 4.1T (Cr/NAA)	Nps Test: BNT, COMP (WAIS-R), LM%, CVLT	-↑Cr/NAA correlated with worse results in BNT and COMP (p<0.05)
Martin et al. [29] (1999)	Correlation with Nps Test	*N*=46 (*n*=32 left MTS vs. *n*= 14 right MTS) age onset left MTS (11.8 y) vs. right MTS (18.7 y)	Ips and ctl hippocampus	Multiple voxel 1H-MRS 4.1T (Cr/NAA)	Nps Test: BNT BFTR VIQ and PIQ (WAIS-R) LM % (WMS)	-↑Cr/NAA in ips hippocampus in MTS (p<0.05) -↑Cr/NAA in left hippocampus negatively correlated with BNT (p<0.004) and LM% (p<0.002) -↑Cr/NAA in right hippocampus negatively correlated with BFTR (p<0.02) -↑Cr/NAA in ips hippocampus in MTS (p<0.05)
Namer et al. [30] (1999)	Correlation with seizures and memory	*N*=39 (*n*=14 left MTS vs. *n*=13 right MTS vs. *n*=12 c)	Ips and ctl hippocampus	Single voxel 1H-MRS, 3.0T (Cho, Cr, (NAA/Cho+Cr))	T2 relaxation test Nps: WAIS-R, WMS, ELI, Engel	-↓ NAA/(Cho+Cr) in ips and ctl hippocampus in MTS (p<0,05) -↓NAA/(Cho+Cr) in ips hippocampus negatively correlated with frequency of seizures (p=0.002). -↓NAA/(Cho+Cr) + T2 relaxation in left hippocampus correlated with verbal memory (p=0.021) -↓NAA/(Cho+Cr) + T2 relaxation in right hippocampus correlated with global (p=0.017), visual (p=0.002), and delayed memory (p=0.007).
Woermann et al. [31] (1998)	Evaluation of spectroscopic differences	*N*=45 (*n*=15 MTS vs. *n*=15 n-MTS vs. *n*=15 c) age onset MTS (5 y) vs. n-MTS (15 y).	Ips and ctl hippocampus	Single voxel 1H-MRS 1.5T (NAA, Cr, Cho, Glx, mI, NAA/(Cho+ Cr) NAA/mI, NAA/Glx)		-↓NAA (p<0.001), NAA/Ins, and NAA/Cr in ips hippocampus in MTS vs. n-MTS -↓NAA/Glx in ips and ctl hippocampus in MTS vs. c (p<0.001) -↓NAA/Glx in ips hippocampus ips vs. ctl in n-MTS vs. MTS (p<0.001) -↑Glx in ips hippocampus in n-MTS (p<0.05)
Duc et al. [32] (1998)	Correlation MRS with histopathology and postsurgical symptoms	*N*=22 (*n*=11 MTS vs. *n*= 11 c)	Ips and ctl hippocampus	Single voxel 1H-MRS 1.5T (NAA, Cr, Cho)	HP, Engel	-↓NAA in ips (p<0.001) and ctl (p<0.03) hippocampus. -↓NAA in ips hippocampus correlated with sclerosis in HP (p<0.001) -↓NAA in ips hippocampus correlated with age onset (p<0.01)

Table 1 (continued)

Author/year	Objectives	Design	Region	MRS	Additional test	Results
Conelly et al. [33] (1998)	Evaluation of spectroscopic differences	*N*=35 (*n*=15 MTS vs. *n*=7 n-MTS vs. *n*=13 c)	Ips and ctl hippocampus	Single voxel 1H-MRS 1.5T NAA, Cr, Cho, NAA/(Cho+Cr)		-↓NAA in ctl hippocampus ctl longer duration of epilepsy (p<0.001) -↓NAA/(Cho+Cr) in *n*=5 n-MTS (2 with bilat changes)

AF|NAA|: Asymmetry factor of N-acetylaspartate; tATP: ATP total; AIGB: anterior insula-basal ganglia; AHIP: anterior hippocampus; BNT: Boston Naming Test; Cho: choline; COMP: comprehension subtest of the Wechsler Adult Intelligence Scale; C: controls; Ctl: contralateral; Cr: creatinine; CSI: chemical shift imaging; CVLT: California Verbal Learning Test; ELI: Edinburg laterality and inventory; MTS: mesial temporal sclerosis; Glx: glutamate+glutamine; HP: histopathology; IQ: intelligence quotient; Ips: ipsilateral; LM%: Wechsler Scale Logical Memory per cent retention; MHIP: middle of hippocampus; mI: mioinositol; NAA: N-acetylaspartate; PCr: phosphocreatine; PDE: phosphodiesterase; Pi: phosphate inorganic; PIGB: posterior insula-basal ganglia; PME: phosphomonoesters; PHIP: posterior hippocampus; PSz: persistent seizures; RAVLT: Rey Auditory Verbal Learning Test; SzF: seizure free; Refract: refractory to medical treatment; tNAA: N-acetylaspartate+N-acetylglutamate; Nps Test: neuropsychological test; Video-EEG: video-encephalogram; WAIS-R: Wechsler Adults Intelligence Scale Revised; WM: white matter; 1H-MRS: proton magnetic resonance spectroscopy; 31P-MRS: phosphorus magnetic resonance spectroscopy

The decrease in NAA can be detected in different ways, for example, measuring just NAA or determining its different ratios. The ratios that are most altered are NAA/Cho+Cr and NAA/Cr. However, when a decrease is detected in NAA/Cho+Cr or NAA/Cr, it is questioned whether the ratio is reduced due to theoretical high levels of Cr or Cho (which are in the denominator of the ratio, so an increase in their levels could result in a decrease of the ratio) instead of altered NAA levels. Accordingly, it is necessary to obtain the individual results of Cr and Cho, as did the studies summarized in Table 1.

In most studies, patients with MTS did not show a statistically significant alteration in Cr or Cho levels [12, 13, 16–22, 27, 30–37, 40]. The only exception was the study by Riederer et al. [15], in which Cr was decreased, contrary to what was expected. However, this study admitted a few limitations in spectroscopic data acquisition due to artifacts of bone and air from areas adjacent to the selected voxel.

Comparative studies in extrahippocampal regions

MTS may affect other brain regions outside the hippocampus, as seen in several of the studies included in our systematic review. A decrease in NAA levels was detected in frontal and occipital lobes [36], thalamus [39], temporal operculum, cerebellum, insula [21], and temporal lobe white matter of the ipsilateral side [13, 27]. In addition, Park et al. [10] noted that additional mitochondrial products such as inorganic phosphate and the PCr/γ-ATP were decreased in the insula and basal ganglia using 31-MRS. In 9 studies, NAA was decreased on the contralateral side, and the most altered region on this side was the hippocampus [12, 15, 18, 20, 31, 32, 34, 35, 39].

Studies in which MRS was performed for surgical evaluation

Eleven studies found a decrease in NAA, NAA/Cho+Cr, and NAA/Cr ratios in presurgical evaluation [12, 14–16, 18–22, 25, 40].

MRS was performed as postsurgical evaluation in 2 studies, which concluded that the damage produced by MTS could be caused by functional and dynamic mechanisms. Spencer et al. [35] only included postsurgical MRS, while Lantz et al. [34] analyzed spectroscopic data obtained both before and after surgery.

Lantz et al. [34] noted that patients with MTS who responded to surgical treatment showed MRS normalization of the contralateral abnormalities detected in the preoperative evaluation, with NAA values almost reaching those found in healthy subjects. This suggests that the decrease in NAA could be reversible and modified by such treatment as hippocampal resection. Also, postoperative normalization was more

pronounced for patients showing an extensive decrease in NAA [34]. The explanation for this is still unknown. However, postsurgical normalization in MRS could be more appreciable in patients who have instability in their clinical condition and their metabolic state, so they have more room for improvement as compared to patients with disease restricted mainly to the hippocampus. If this association is correct, presurgical MRS could allow the selection of patients who could benefit more from hippocampal resection.

Comparative MRS studies with clinical characteristics and epileptiform activity on EEG

Concerning the possible association between MRS and seizures, 6 studies showed that lower NAA correlated with an early onset age of the symptoms [32], longer duration of epilepsy [20, 32, 37], greater frequency of seizures [30], and epileptogenic activity on EEG on the ipsilateral and contralateral sides [20].

Focusing on studies which evaluated the response to surgery, Spencer et al. [35] noted that patients with a higher frequency of seizures after surgery presented more brain regions with low NAA in postsurgical MRS. Therefore, postsurgical MRS could predict the long-term response in patients with MTS, although comparative studies with MRS evaluation before and after surgery are necessary.

MRS studies that included neuropsychological evaluation

One of the most common and disabling symptoms in MTS is dysfunction in verbal memory, more severe in patients with left MTS. Four studies detected a decrease in NAA [24, 28, 29] and a decrease in NAA/Cho+Cr [37] in patients with a worse performance in verbal memory tests.

Regarding patients with right MTS, no cognitive deficiencies related to verbal memory could be detected, except in the study of Mantoan et al. [37], in which patients with right MTS who had low NAA/Cho+Cr levels in the left hippocampus had worse scores in verbal memory.

Finally, Martin et al. [29] included facial recognition tests, with the worst scores detected in patients with a decrease in NAA in the right hippocampus.

Comparative studies of patients with and without sclerosis

Several comparative studies included in this review noted that, as well as MTS, n-MTS patients also presented a decrease in NAA [12, 19, 38] and a decrease in NAA/Cho+Cr [40], in the ipsilateral hippocampus, although NAA was even lower in the MTS patients.

According to some studies, to distinguish between MTS and n-MTS, we should focus on other metabolites. The most striking difference was in the level of Glx, which was significantly increased in 2 studies. Woermann et al. [31] found this in the ipsilateral hippocampus and Simister et al [22] detected it on the contralateral side. However, Doelken et al. [38] and Riederer et al. [15] did not find any significant alteration in Glx in n-MTS patients. Though more studies including this metabolite are necessary, Glx could possibly differentiate between MTS and n-MTS.

Regarding mI, the results from 6 studies were conflicting; 4 found no statistically significant differences between MTS and n-MTS [12, 13, 22, 38]. On the other hand, Riederer et al. [15] noted that n-MTS patients presented a lower mI/Cr ratio than MTS patients, while Mueller et al. [19] only detected low mI levels in MTS patients.

Single voxel and multiple voxel MRS

Single voxel MRS was performed in 18 studies [12–18, 20, 25, 27, 28, 30–33, 37–39], proving technically easier to analyze the hippocampus. Patients with MTS were evaluated using multiple voxel in the remaining 12 studies [10, 19, 21–24, 26, 29, 34–36, 40], mainly used to study extrahippocampal regions in which it could be difficult to place the voxel due to the absence of structural abnormalities on MR [9]. However, none of these studies compared single and multiple voxel MRS in patients with MTS.

Limitations and future lines

The main limitations of the studies analyzed in this review were the heterogeneity in the MRS technique, the sample sizes, and the characteristics of the population. We included only two studies performed MRS after surgery, so it is not possible to conclude the usefulness of MRS in post-surgical evaluation. Accordingly, this field requires further studies that include presurgical and postsurgical MRS evaluation in a larger sample size to understand the main reasons for the postoperative normalization in the contralateral hippocampus. In addition, it is necessary to establish a protocol for MRS evaluation, using the same ratio of NAA in order to accurately compare between different studies. Future studies all need to include quantitative and qualitative variables such as the frequency of seizures, onset age, duration of epilepsy, and epileptogenic activity on EEG. Only then will we be able to determine the possible association between these variables and MRS. In addition, measurement of other metabolites such as Glx and mI is also required in the MRS evaluation.

Conclusions

This systematic review shows that, in most MRS studies, patients with MTS presented a decrease in NAA in the ipsilateral hippocampus. Furthermore, the decrease in NAA could be detected in extrahippocampal regions on the ipsilateral and the contralateral sides. Additionally, comparative studies also presented NAA decreased in the ipsilateral hippocampus in n-MTS patients. Thus, MRS could be useful but not specific for the diagnosis of MTS and could have a role in the presurgical evaluation to locate the epileptogenic focus. However, further research in this field is needed.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards

Informed consent Informed consent was obtained from all individual participants included in the study.

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