Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Magnetic Resonance Spectroscopy and Metabolic MRI in Epilepsy: A Systematic Review and Quantitative Synthesis of Neurochemical Biomarkers and Clinical Applications

Sama Rahnemayan
Medical University of Vienna: Medizinische Universitat Wien https://orcid.org/0000-0003-0641-4178
Sanne Schins
Maastricht University Medical Centre https://orcid.org/0000-0002-4478-5298
Philipp Lazen
Medical University of Vienna https://orcid.org/0000-0002-9952-3084
Jabrane Karkouri
University of Cambridge https://orcid.org/0000-0002-3857-0119
Karl Rössler
Medical University of Vienna https://orcid.org/0000-0002-9249-8082
Tatjana Traub-Weidinger
Medical University of Vienna https://orcid.org/0000-0003-1118-926X
Isabel Pugna
Medical University of Vienna https://orcid.org/0009-0003-1465-4072
Thomas Nakuz
Medical University of Vienna https://orcid.org/0000-0002-9191-5235
Stefanie Chambers
Medical University of Vienna https://orcid.org/0009-0002-6420-1154
Wolfgang Bogner
Medical University of Vienna https://orcid.org/0000-0002-0130-3463
Roxane Licandro
Medical University of Vienna https://orcid.org/0000-0001-9066-4473
Silvia Bonelli
Medical University of Vienna https://orcid.org/0000-0002-6346-8474
Evita Wiegers
University Medical Center Utrecht https://orcid.org/0000-0001-5451-2990
Christopher T Rodgers
University of Cambridge https://orcid.org/0000-0003-1275-1197
Jacobus FA Jansen
Maastricht University Medical Centre https://orcid.org/0000-0002-5933-4676

Maxime Guye
Aix-Marseille University https://orcid.org/0000-0002-4435-2257
Esin Ozturk-Isik
Boğaziçi University https://orcid.org/0000-0002-8997-878X
Gilbert Hangel
gilbert.hangel@meduniwien.ac.at
Medical University of Vienna https://orcid.org/0000-0002-3986-3159

Systematic Review

Keywords: Epilepsy, Magnetic Resonance Spectroscopy, Metabolic MRI. Chemical Exchange Saturation Transfer, Sodium MRI, Phosphorus Magnetic Resonance Spectroscopy, Deuterium Metabolic Imaging

Posted Date: November 3rd, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11592816/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: The authors declare no competing interests.

Magnetic Resonance Spectroscopy and Metabolic MRI in Epilepsy: A Systematic Review and Quantitative Synthesis of Neurochemical Biomarkers and Clinical Applications

Authors

Sama Rahnemayan,[1,2] Sanne Schins,[3,4] Philipp Lazen,[1,2] Jabrane Karkouri,[5] Karl Rössler,[1] Tatjana Traub-Weidinger,[6] Isabel Pugna,[6,7,8] Thomas Nakuz,[6] Stefanie Chambers,[6] Wolfgang Bogner,[2,9,10] Roxane Licandro,[11] Silvia Bonelli,[7,8] Evita Wiegers,[12] Christopher T Rodgers,[5] Jacobus FA Jansen,[3,4,13] Maxime Guye,[14] Esin Ozturk-Isik,[15,16] Gilbert Hangel[1,2,9*]

on behalf of the EPICONN consortium

[1] Department of Neurosurgery, Medical University of Vienna, Vienna, Austria

[2] High-Field MR Centre, Department of Biomedical Imaging and Image-guided Therapy, Medical University of Vienna, Vienna, Austria

[3] Department of Radiology & Nuclear Medicine, Maastricht University Medical Center, Maastricht, The Netherlands

[4] Mental Health and Neuroscience Research Institute (MHeNs), Maastricht University, Maastricht, Netherlands

[5] Wolfson Brain Imaging Centre, Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK

[6] Department of Biomedical Imaging and Image-Guided Therapy, Medical University of Vienna, Vienna, Austria

[7] Department of Neurology, Medical University of Vienna, Waehringer Guertel 18-20, 1090 Vienna, Austria

[8] Comprehensive Center for Clinical Neurosciences and Mental Health, Medical University of Vienna, Vienna, Austria

[9] Christian Doppler Laboratory for MR Imaging Biomarkers (BIOMAK), Medical University of Vienna, Vienna, Austria

[10] Comprehensive Center for AI in Medicine (CAIM), Medical University of Vienna, Vienna, Austria

[11] Department of Biomedical Imaging and Image-guided Therapy, Computational Imaging Research Lab (CIR), Early Life Image Analysis Group, Medical University of Vienna, Vienna, Austria

[12] Center for Image Sciences, University Medical Center Utrecht, Utrecht, Netherlands

[13] Department of Electrical Engineering, Eindhoven University of Technology, Eindhoven, Netherlands
[14] Aix-Marseille University, CNRS, CRMBM, Marseille, France
[15] Institute of Biomedical Engineering, Bogazici University, Istanbul, Türkiye
[16] Bogazici University Center for Targeted Therapy Technologies, Istanbul, Türkiye

Corresponding author:
Gilbert Hangel
Address: Lazarettgasse 14, 1090 Vienna, Austria
Email: gilbert.hangel@meduniwien.ac.at
Phone: +43 (0)1 40400-64710

Declarations

Ethics approval and registration

This study was conducted on previously published material, with no direct patient contact. The protocol is registered on PROSPERO (Registration code: CRD420261371970).

Consent for Publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

Authors declare no conflict of interests.

Funding

This project was funded by the Ludwig Boltzmann Gesellschaft (LBG) as part of the Clinical Research Groups programme, No. LBG_KFG_2024_023. This research was funded in whole, or in part, by the Austrian Science Fund (FWF) grant 10.55776/KLI1121.
CTR is supported by the NIHR Cambridge Biomedical Research Centre [NIHR203312] and the Medical Research Council [UKRI226, UKRI790]. The views expressed are those of the author(s) and not necessarily those of the NIHR, the NHS, or the Department of Health and Social Care. For the purpose of open access, the author has applied a Creative Commons Attribution (CC BY) licence to any Author Accepted Manuscript version arising from this submission.

Authors' contributions

SR: Conceptualization, Methodology, Investigation, Data curation, Writing – original draft, Writing – review & editing.

SS: Investigation, Data curation, Writing – original draft, Writing – review & editing.

EOI, EW, CTR, JFAJ, MG, JK, SBN, RL, KR, TTW, IP, TN, SC, PL, WB: Conceptualization, Methodology, Writing – review & editing.

GH: Conceptualization, Methodology, Supervision, Project administration, Writing – review & editing.

Permissions

Publication licenses for figures created using BioRender were obtained in accordance with BioRender's licensing requirements.

Members of the EPICONN Consortium

Marc Berger, Thomas Berger, Silvia Bonelli-Nauer, Christian Dorfer, Daniel Engler, Florian Ph.S Fischmeister, Gerhard Gritsch, Marcus Hacker, Gilbert Hangel, Gregor Kasprian, Zakia Khatun, Tilmann Kluge, Masa Kovacevic, Leonie Krausgruber, Martin Krenn, Georg Langs, Lukas Lechner, Joel Leinkauf, Roxane Licandro, Daniela Lötsch-Gojo, Thomas Nakuz, Karl-Heinz Nenning, Maximilian Nentwich, Linda Pacher, Ekaterina Pataraia, Hannes Perko, Isabel Pugna, Sama Rahnemayan, Karl Rössler, Martin Tik, Tatjana Traub-Weidinger, Nicolas Weilguny, Verena Witz

Highlights

- Reduced tNAA is the shared metabolic hallmark across focal, generalized, and tumor-associated epilepsies.
- Focal epilepsy exhibits the greatest metabolic heterogeneity, extending beyond the epileptogenic region into distributed brain networks.
- Generalized epilepsies are characterized predominantly by thalamo-cortical neuronal dysfunction, whereas tumor-associated epilepsy is dominated by glutamatergic dysregulation.
- Neurotransmission, gliosis, and bioenergetic markers provide syndrome- and treatment-specific metabolic signatures beyond tNAA.
- Emerging metabolic MRI modalities reveal complementary abnormalities in bioenergetics, ionic homeostasis, and metabolic flux.
- Higher-field and edited MRS extended epilepsy profiling beyond tNAA, revealing region- and pathology-specific alterations in Glu, Gln, and GABA rather than a uniform neurotransmitter signature.

Abstract

Background: Since the introduction of proton magnetic resonance spectroscopy (^{1}H-MRS) in epilepsy research in the 1980s, metabolic MRI has provided unique insights into the neurochemical alterations underlying epilepsy. However, evidence has remained fragmented across imaging modalities, epilepsy syndromes, and clinical applications. We systematically reviewed the literature to define the metabolic phenotype of epilepsy and evaluate the evolving role of metabolic MRI in epilepsy research and clinical practice.

Methods: Following PRISMA 2020 guidelines, PubMed and Scopus were systematically searched through April 2026 for original human studies investigating metabolic MRI in epilepsy. Two reviewers independently performed study selection, data extraction, and quality assessment. Findings were synthesized through structured qualitative evidence, supported by integrated methodological, scientometric, tabular, and visual analyses.

Results: A total of 298 studies were included. Focal epilepsy demonstrated widespread alterations involving N-acetyl aspartate, glutamate, Gamma-aminobutyric acid, choline-containing compounds, myo-inositol, lactate, and other metabolites across epileptogenic and brain networks. Generalized epilepsy was characterized by predominantly bilateral and thalamo-cortical metabolic abnormalities, whereas tumor-associated epilepsy showed distinct metabolic alterations within tumors and the peritumoral zone. Treatment and prognostic studies demonstrated metabolite-specific changes following pharmacological and surgical interventions, and emerging metabolic MRI techniques provided complementary information on bioenergetics, ionic homeostasis, glutamatergic cycling, and metabolic flux.

Conclusions: The available evidence supports epilepsy as a disorder of distributed metabolic networks that share a common signature of neuronal dysfunction while exhibiting syndrome-specific alterations in neurotransmission, gliosis, and energy metabolism. Complementary metabolic MRI techniques provide distinct biological information, but their clinical translation will require methodological harmonization and multimodal integration.

Keywords: Epilepsy; Magnetic Resonance Spectroscopy; Metabolic MRI; Chemical Exchange Saturation Transfer; Sodium MRI; Phosphorus Magnetic Resonance Spectroscopy; Deuterium Metabolic Imaging.

1. Introduction

Magnetic resonance spectroscopy (MRS) and related metabolic MRI techniques extend conventional MRI beyond anatomy by non-invasively characterizing the biochemical composition of brain tissue *in vivo*[1–3]. Unlike structural MRI, which depicts tissue morphology, or functional MRI (fMRI), which measures hemodynamic responses associated with neuronal activity, metabolic MRI quantifies tissue metabolite concentrations or metabolic exchange processes that serve as indirect markers of underlying cellular physiology[4]. Over the past three decades, hundreds of studies have applied these techniques to investigate metabolic alterations in epilepsy. Despite this extensive body of research, the findings have largely been examined within individual epilepsy syndromes, metabolic pathways, or imaging modalities, without a comprehensive systematic synthesis that spans the entire field.

Metabolic MR research in epilepsy has evolved from localized measurements of cerebral bioenergetics and metabolites to increasingly spatial and mechanistic characterization of epileptic networks. The rapid expansion of proton magnetic resonance spectroscopy (^{1}H-MRS) in the 1990s established reduced N-acetylaspartate (NAA), particularly in temporal lobe epilepsy, as a characteristic finding and stimulated interest in metabolic lateralization of the epileptogenic region[5–8]. Subsequent magnetic resonance spectroscopic imaging (MRSI) studies demonstrated that metabolic abnormalities could extend beyond the presumed epileptogenic region into contralateral and more widespread regions[9,10], while longitudinal studies showed partial normalization after successful surgery, supporting a potentially reversible component of metabolic dysfunction[8,11–14]. More recent high-field and broader metabolic imaging approaches have increasingly shifted the field toward characterization of distributed metabolic networks and a wider range of neurochemical processes[15,16].

During the last decade, metabolic MRI has emerged from conventional ^{1}H-MRS into a family of related techniques with different but partially overlapping capabilities to assess brain metabolism *in vivo*[17]. Apart from ^{1}H-MRS, ^{31}P-, ^{13}C-, and ^{23}Na-MRS, chemical exchange saturation transfer (CEST), and deuterium metabolic imaging (DMI) are also currently used to study cerebral energetics, intermediary metabolism, signaling processes, and ionic homeostasis[18]. Each of these approaches is sensitive to specific aspects of brain physiology and pathophysiology, providing a complex but limited set of metabolic parameters indirectly related to neural activity through measures of cerebral metabolites or, in CEST, through chemical exchange between solute protons and bulk water[19]. Despite the reported involvement of various metabolic and ionic processes in the pathogenesis of epilepsy, the literature data remain conflicting and do not allow a confident conclusion regarding the presence or absence of common metabolic biomarkers of epilepsy[20].

Studies have reported abnormalities in neuronal integrity, energy metabolism, neurotransmission, glial metabolism, ionic homeostasis, and other processes across different epilepsy syndromes and forms of focal epilepsy[18,21]. Each of the studies evaluated specific aspects of brain metabolism and function using different methodologies and approaches, while interpreting the results in the context of particular epilepsy syndromes, theoretical frameworks, or network organization. Accordingly, the question whether the reported diverse metabolic alterations in epilepsy represent different aspects of a unitary correlation of the disease needs clarification[22].

This is especially important given the notion of epilepsy as a connectopathy, where structural MRI reflects epileptic networks at the level of anatomical connectivity, whereas electroencephalography and fMRI represent functional connectivity[23]. The metabolism-related MRI studies of epilepsy lie between fMRI and structural MRI, probing the altered network organization at the level of the function of individual nodes[24]. Specifically, metabolic MRI can provide important insights into the basic mechanisms of connectopathy by characterizing the alterations in cerebral metabolism that underlie the changes in the function of individual nodes participating in epileptic networks[25]. These spatially distributed metabolic alterations may also have functional consequences, with regional metabolite abnormalities being associated with cognitive functions, such as memory, language, and executive performance.

Although the individual metabolic measures are not specific for a single component of connectopathy, reflecting a confluence of different processes, each of the alterations detected indicates a potential disruption of normal physiology[24]. The metabolic MRI findings can be used as a valuable complement to the data from structural and functional MRI, the evaluation of their functional status, the characterization of network-specific ionic homeostasis, and the analysis of epilepsy-associated alterations of metabolism with respect to potential therapeutic interventions[26].

The goal of our systematic review was to determine whether the results of metabolic MRI studies of epilepsy point to the existence of common metabolic biomarkers of the disease. Rather than considering individual findings in isolation, we examined whether consistent patterns emerge across different metabolites, epilepsy types, brain regions, and imaging approaches despite the heterogeneity of the literature. We further evaluated how these patterns relate to epileptic network organization and the cognitive and clinical correlates of these patterns, with the aim of identifying the core metabolic endophenotypes of epilepsy.

2. Methods

2.1 Study design and protocol

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement[27], and the review protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO)[28].

2.2 Literature search

We performed a comprehensive electronic search of PubMed and Scopus databases for original articles investigating metabolic MRI in epilepsy. The initial search was conducted in April 2026, and the search strategy comprised MeSH terms and free-text terms related to the topic of interest. The search strategy also included specialized search strategies for CEST MRI, deuterium metabolic imaging, and sodium MRI to ensure all relevant studies were identified. The complete search strategies are provided in Supplementary file.

In addition, we performed manual searches of reference lists of all included studies, and we also conducted a Google Scholar search to identify any additional studies that may have been missed in the electronic search.

2.3 Eligibility criteria

The inclusion criteria were as follows: the study population had to contain patients with epilepsy or epileptic syndromes; the study had to utilize metabolic magnetic resonance methods, specifically ^{1}H-MRS, ^{31}P-MRS, ^{13}C-MRS, or ^{23}Na MRI, CEST, or DMI; the study had to report original research; the study had to have been published as a full-text article in a peer-reviewed journal in English.

The exclusion criteria were as follows: review articles, systematic reviews, meta-analyses, editorials, letters to the editor, conference abstracts, comments, case reports, or animal studies were excluded; studies examining animal models of seizures or epilepsy, *in vitro* studies, studies primarily focused on inherited metabolic diseases, isolated genetic epilepsy syndromes or other non-epileptic conditions, or studies that failed to report original metabolic MRI findings pertinent to epilepsy were also excluded. In cases of multiple publications from the same study population, the publication with the most comprehensive data was included.

2.4 Study selection

All publications identified in the search were uploaded to Rayyan for screening and duplicate removal[29]. Following the completion of the deduplication process, two independent reviewers

applied the inclusion/exclusion criteria by screening the titles and abstracts of the remaining publications. The articles identified as potentially eligible by the reviewers were subjected to full-text screening by the same two reviewers. Discrepancies at both stages were resolved through discussion until a consensus was reached.

2.5 Data extraction

The data extraction process was carried out independently by two reviewers using a predesigned data extraction form. For each publication, the following data were extracted: publication details; study design; country; objectives; population; epilepsy syndrome; MRI method; spectroscopy acquisition details; field strength; acquisition details; metabolites and ratios quantified; image processing and quantification; examined brain regions; main findings and treatment; diagnostic; pathophysiological; prognostic; or cognitive relevance reported in the study. The extracted data were used to populate evidence synthesis tables and figures, perform scientometric analyses, carry out methodological quality assessments, and prepare summary tables and figures. Following the data extraction, any disagreements between the two reviewers were resolved through discussion until a consensus was reached.

2.6 Methodological quality assessment

Two independent reviewers assessed the methodological quality of the included studies using two different sets of quality assessment tools. Specifically, the overall methodological quality of the studies was assessed using the Mixed Methods Appraisal Tool (MMAT, version 2018)[30]. The Magnetic Resonance Spectroscopy Quality (MRS-Q) assessment tool was used to evaluate the methodological quality and reporting of spectroscopy-specific aspects[31]. The MMAT assessment criteria included design appraisal, participants, data collection and management, outcome measurement, confounding, and analysis[30], whereas the MRS-Q assessment criteria comprised recommendations pertinent to spectroscopy acquisition, preprocessing, quantification, spectral quality assessment, and reporting[31]. Discrepancies between the two reviewers were resolved through discussion until a consensus was reached.

2.7 Scientometric analysis

A descriptive scientometric analysis was conducted using the extracted data. Specifically, the number of publications per year, country, objectives, MRI method, spectroscopy acquisition type, field strength, examined metabolites, and reporting specifics were determined and visualized. Due to the timing of the search, publications that appeared in 2026 were excluded

from the analysis of publication trends. All figures were generated using custom scripts in Python (version 3.12) with the pandas, numpy, and matplotlib packages[32].

2.8 Data synthesis

Due to the considerable diversity of the population, epilepsy syndrome, MRI methods, acquisition, imaging parameters, metabolites, analytical approaches, and reports among the included studies, we opted to perform a narrative synthesis of the evidence rather than a quantitative one. First, the included studies were grouped according to the MRI methods utilized (^{1}H-MRS *vs* non ^{1}H-MRS). Within the ^{1}H-MRS category, the literature was further stratified according to the epilepsy subtypes investigated (focal epilepsy, generalized epilepsy, mixed focal/generalized epilepsy populations, and tumor-associated epilepsy). Within focal epilepsy, the studies were classified depending on their primary objective or application: localization; diagnosis/pathophysiology; cognitive; treatment-related; and prognosis. Furthermore, where relevant to the specific category, the studies were additionally stratified based on the acquisition type: single-voxel spectroscopy (SVS); MRSI; *ex vivo* spectroscopy; and whole-brain MRS. This hierarchical classification allowed the studies with similar characteristics to be grouped together and facilitated the synthesis of findings across studies. Evidence synthesis tables and figures were generated to summarize the findings pertaining to specific brain regions and applications and highlight overall trends in the field.

3. Results/Findings

3.1 Study selection

The extensive search of the databases for this study yielded 2630 records. From these records, 807 duplicates were excluded, leading to 1823 articles being screened against the inclusion criteria. From the 1823 articles, 387 met the inclusion criteria for further full-text screening. Finally, there were 299 studies included in the qualitative study. The selection process of selection is illustrated in Figure 1.

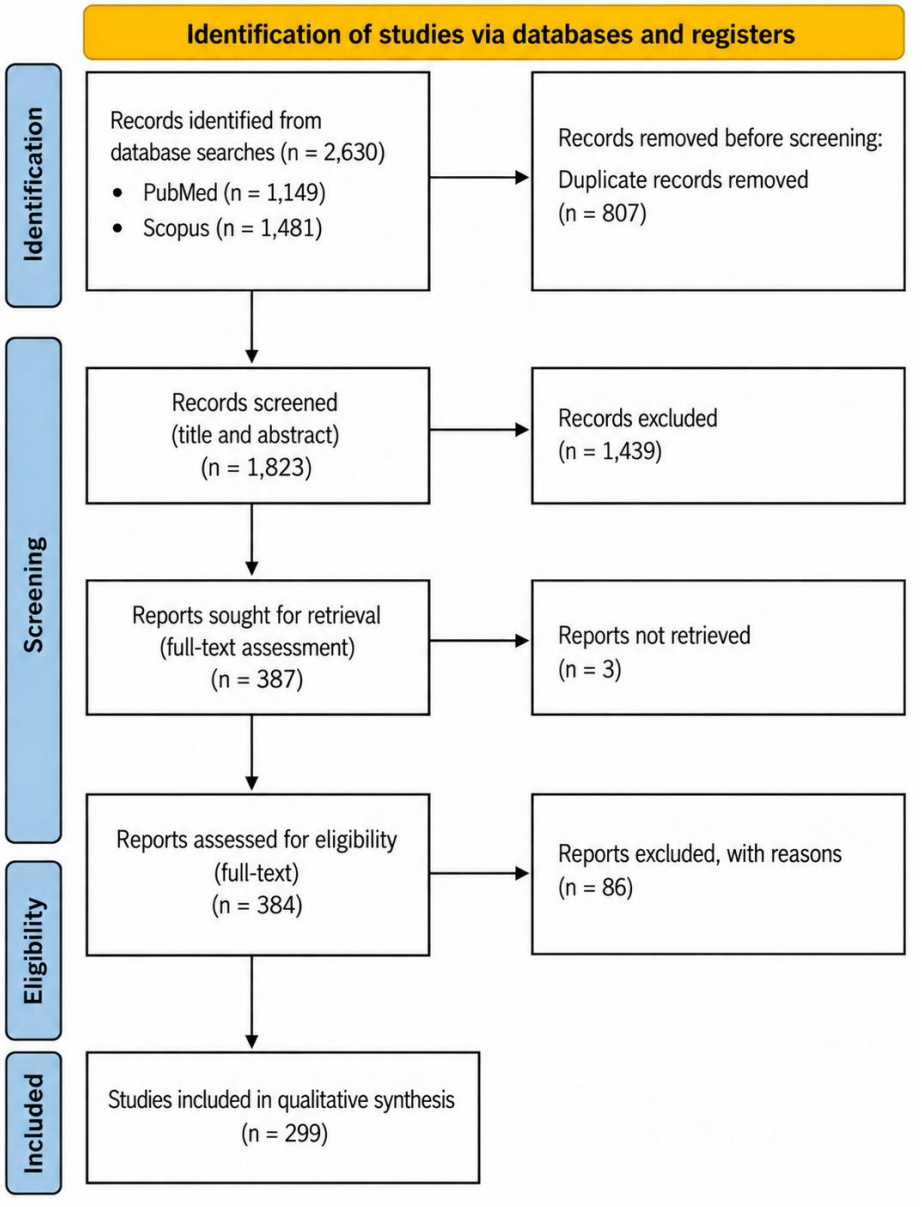


Figure 1. PRISMA 2020 flow diagram illustrating the study selection process for the systematic review.

3.2 Characteristics of included studies

Among the included studies, 83.6% were observational, while 16.4% were interventional (Figure 2). The number of participants per study was generally limited, with a right-skewed distribution, as most of the studies had fewer than 50 patients each. Temporal lobe epilepsy was the most common focus of investigation, accounting for 165 (55.4%) of all the included studies. There were 69.8% of the studies that involved only adults, while 22.8% of the studies involved mixed groups of adult and pediatric patients, and 7% of studies focused solely on pediatric patients.

SVS was the most common MRS selection scheme, which was used in 164 of the included studies versus MRSI in 119 studies. *Ex vivo* spectroscopy was used in nine papers. The Point RESolved Spectroscopy (PRESS) technique was the most common way to excite protons, used in 180 papers, while Image-Selected *In vivo* Spectroscopy (ISIS), Free Induction Decay (FID), Stimulated Echo Acquisition Mode (STEAM), spin-echo, and other specialized techniques were used less frequently.

For the purposes of this review, metabolite measurements that did not explicitly separate their containing compounds were considered total rates. Total NAA (tNAA), total creatine (tCr), and total choline (tCho) were the most frequently measured metabolites in the included studies, while glutamate (Glu), glutamine (Gln), Gamma-Aminobutyric Acid (GABA), myo-inositol (mI), lactate, and others were rarely detected. In addition, tNAA/tCr was the most commonly used ratio, followed by tCho/tCr, tNAA/tCho, tNAA/(tCho+tCr), while other ratios were rarely used.

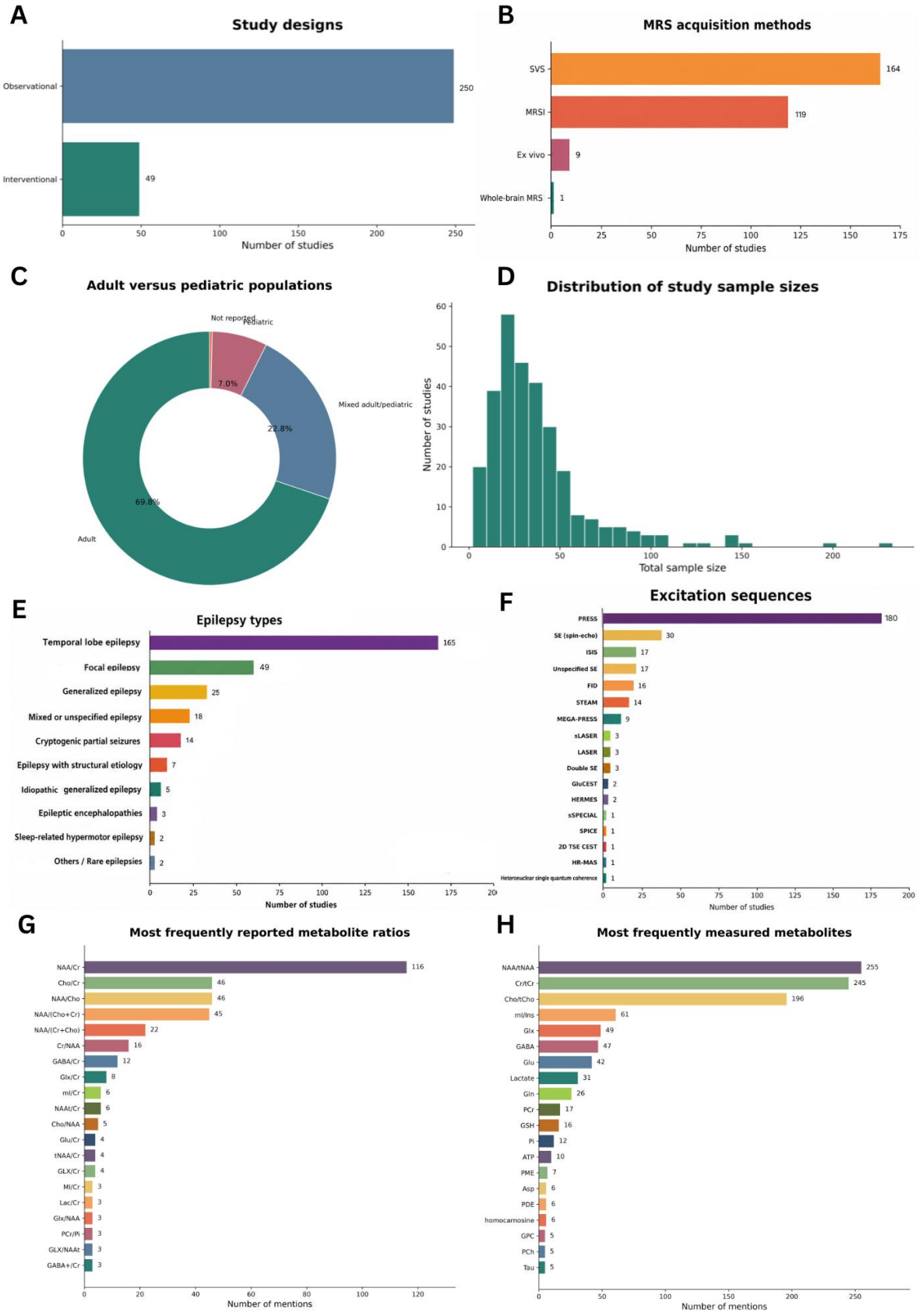


Figure 2. Study and imaging characteristics of the included studies. (A) Distribution of study designs (observational versus interventional). (B) MRS acquisition methods, including

single-voxel spectroscopy (SVS), magnetic resonance spectroscopic imaging (MRSI), ex vivo spectroscopy, and whole-brain MRS. (C) Distribution of study populations by age group (adult, pediatric, mixed adult/pediatric, and not reported). (D) Distribution of study sample sizes. (E) Epilepsy types investigated across the included studies. (F) Distribution of MRS excitation sequences. (G) Most frequently reported metabolite ratios. (H) Most frequently measured metabolites. Bar values indicate the number of studies or mentions, as applicable. Abbreviations: SVS: single-voxel spectroscopy; MRSI: magnetic resonance spectroscopic imaging; MRS: magnetic resonance spectroscopy; PRESS: Point-RESolved Spectroscopy; SE: spin echo; ISIS: Image-Selected *In Vivo* Spectroscopy; FID: free induction decay; STEAM: stimulated echo acquisition mode; MEGA-PRESS: MEscher–GArwood Point-RESolved Spectroscopy; sLASER: semi-localized by adiabatic selective refocusing; LASER: localization by adiabatic selective refocusing; GluCEST: glutamate chemical exchange saturation transfer; HERMES: Hadamard encoding and reconstruction of MEGA-edited spectroscopy; sSPECIAL: semi-adiabatic spin-echo full-intensity acquired localized spectroscopy; SPICE: spectroscopic imaging by exploiting spatiospectral correlation; 2D: two-dimensional; TSE: turbo spin echo; CEST: chemical exchange saturation transfer; HR-MAS: high-resolution magic angle spinning; tNAA: total N-acetylaspartate; Cr: creatine; tCr: total creatine; Cho: choline; tCho: total choline; mI: myo-inositol; Ins: inositol; Glx: glutamate plus glutamine; GABA: γ-aminobutyric acid; Glu: glutamate; Gln: glutamine; PCr: phosphocreatine; GSH: glutathione; Pi: inorganic phosphate; ATP: adenosine triphosphate; PME: phosphomonoesters; Asp: aspartate; PDE: phosphodiesters; GPC: glycerophosphocholine; PCh: phosphocholine; Tau: taurine; Lac: lactate; GLX: glutamate plus glutamine.

3.3 Scientometric analysis

The scientometric analysis of the included studies revealed fluctuations in MRS epilepsy research activity over the past three decades, with an initial peak in publications followed by a decline and a gradual increase in more recent years, alongside increasing methodological diversity and improved reporting quality (Figure 3). The United States was the leading contributor, followed by Europe, Canada, China, and Japan. Median study sample size increased over time, with studies published after 2020 generally enrolling larger cohorts than earlier investigations.

Research priorities evolved considerably throughout the study period. Pathophysiological investigations consistently predominated, while localization studies were particularly common during the 1990s. More recent years showed increasing emphasis on prognostic and cognitive applications. Throughout the literature, 1H-MRS remained the dominant imaging modality, with SVS consistently representing the most frequently used acquisition technique and MRSI showing progressively greater adoption. A parallel transition from scanners below 3T to

predominantly 3T systems was observed after 2010, whereas ultra-high-field (≥7T) imaging emerged only in recent years.

tNAA, tCr, and tCho were consistently the most investigated metabolites, while Glu and Gln were more studied in most recently. Reporting of key methodological parameters—including field strength, echo time (TE), repetition time (TR), voxel size, and metabolite quantification—was consistently high and generally improved over time, although reporting of spectral quality metrics and Chemical Shift Imaging (CSI)-specific parameters remained less complete.

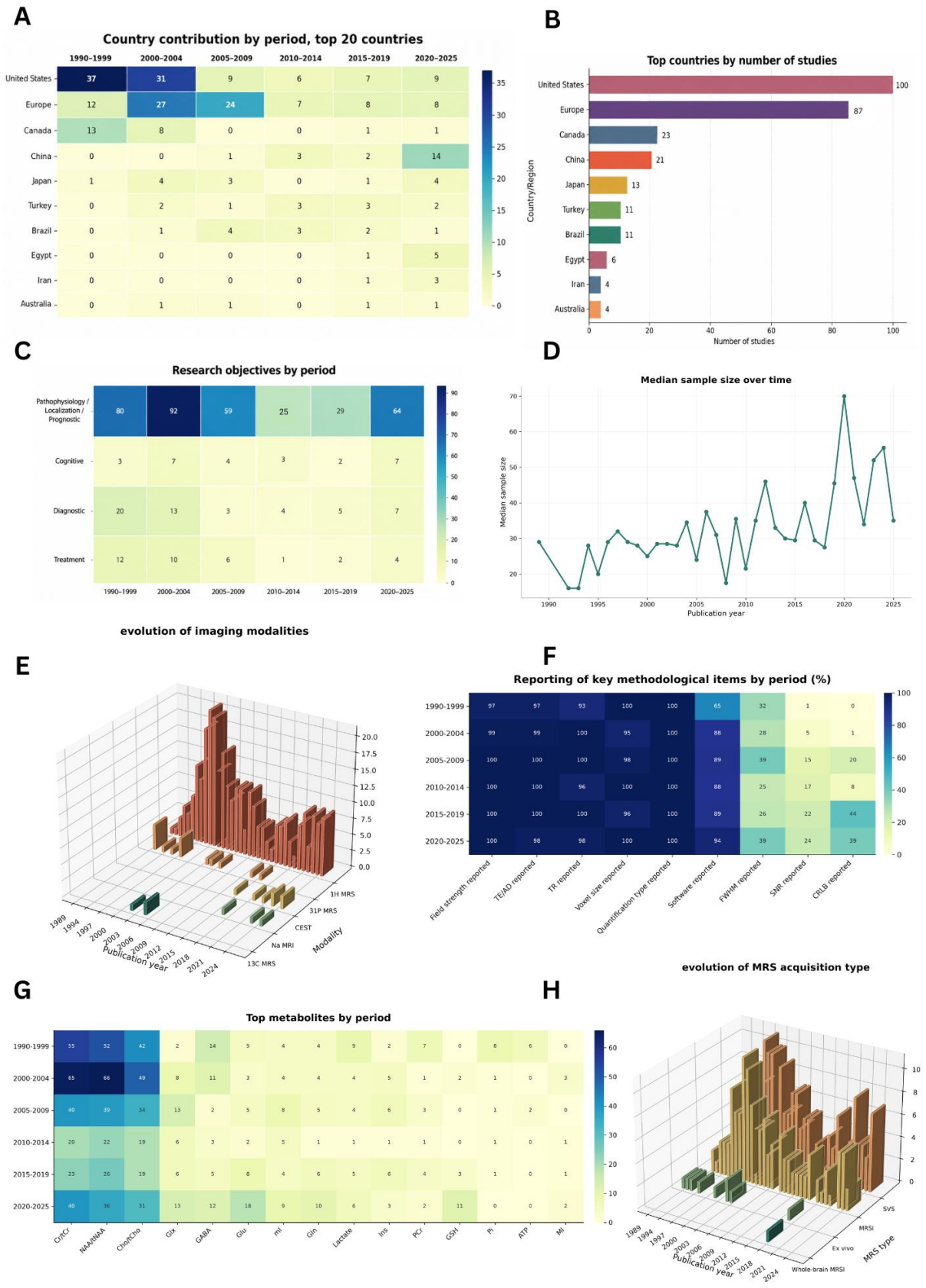


Figure 3. Bibliometric and methodological trends across the included studies. (A) Country and regional contributions across publication periods from 1990 to 2025. (B) Countries and regions contributing the highest numbers of studies. (C) Distribution of research

objectives across publication periods, including pathophysiology/localization/prognosis, cognitive assessment, diagnosis, and treatment. (D) Changes in median study sample size by publication year. (E) Temporal evolution of metabolic imaging modalities, including ^{1}H-MRS, ^{31}P-MRS, chemical exchange saturation transfer (CEST), ^{13}C-MRS, and sodium MRI. (F) Reporting frequencies of key methodological parameters across publication periods. (G) Temporal distribution of the most frequently investigated metabolites. (H) Evolution of MRS acquisition methods, including single-voxel spectroscopy (SVS), magnetic resonance spectroscopic imaging (MRSI), ex vivo spectroscopy, and whole-brain MRSI. Abbreviations: MRS: magnetic resonance spectroscopy; ^{1}H MRS: proton magnetic resonance spectroscopy; ^{31}P MRS: phosphorus-31 magnetic resonance spectroscopy; ^{13}C MRS: carbon-13 magnetic resonance spectroscopy; Na MRI: sodium magnetic resonance imaging; CEST: chemical exchange saturation transfer; SVS: single-voxel spectroscopy; MRSI: magnetic resonance spectroscopic imaging; FWHM: full width at half maximum; SNR: signal-to-noise ratio; CRLB: Cramér–Rao lower bounds; tNAA: total N-acetylaspartate; Cr: creatine; tCr: total creatine; Cho: choline; tCho: total choline; Glx: glutamate plus glutamine; GABA: γ-aminobutyric acid; Glu: glutamate; mI: myo-inositol; Gln: glutamine; Ins: inositol; PCr: phosphocreatine; GSH: glutathione; Pi: inorganic phosphate; ATP: adenosine triphosphate.

3.4 Methodological quality assessment

The included studies were mostly of high methodological quality according to the MMAT, with 72.1% high, 27.9% moderate, and 0% low-quality studies (Figure X). Most of the included studies adequately formulated their research question, used the correct measurements, and reported all the required data for the selected methods while only 41.2% had representative samples and 63.1% controlled all the relevant confounders.

Compliance with the MRS-Q criteria varied significantly, with 13.7%, 61.5%, and 24.8% of the studies achieving high, moderate, and low MRS-Q scores, respectively (Figure 4). Indeed, the MRS-Q compliance was high for sequence selection (86.5%), preprocessing and analysis methods (95.6%), and frequency/phase correction when required (82.2%). However, the studies had a low compliance with recommendations on field strength (36.5%), acquisition parameters (52.6%), partial volume correction (35.9%), scanner drift assessment (26.8%), and power calculation (6.4%). These results should be interpreted with caution, as MRS-Q was applied retrospectively and beyond its intended scope to assess a heterogeneous body of literature, including studies that employed spectral editing. In particular, field-strength recommendations are technique-dependent and cannot be used as a general indicator of methodological quality across different MRS approaches. Moreover, lower MRS-Q scores do

not necessarily indicate poor methodological quality but may reflect differences in technical requirements or the absence of current reporting standards at the time of publication.

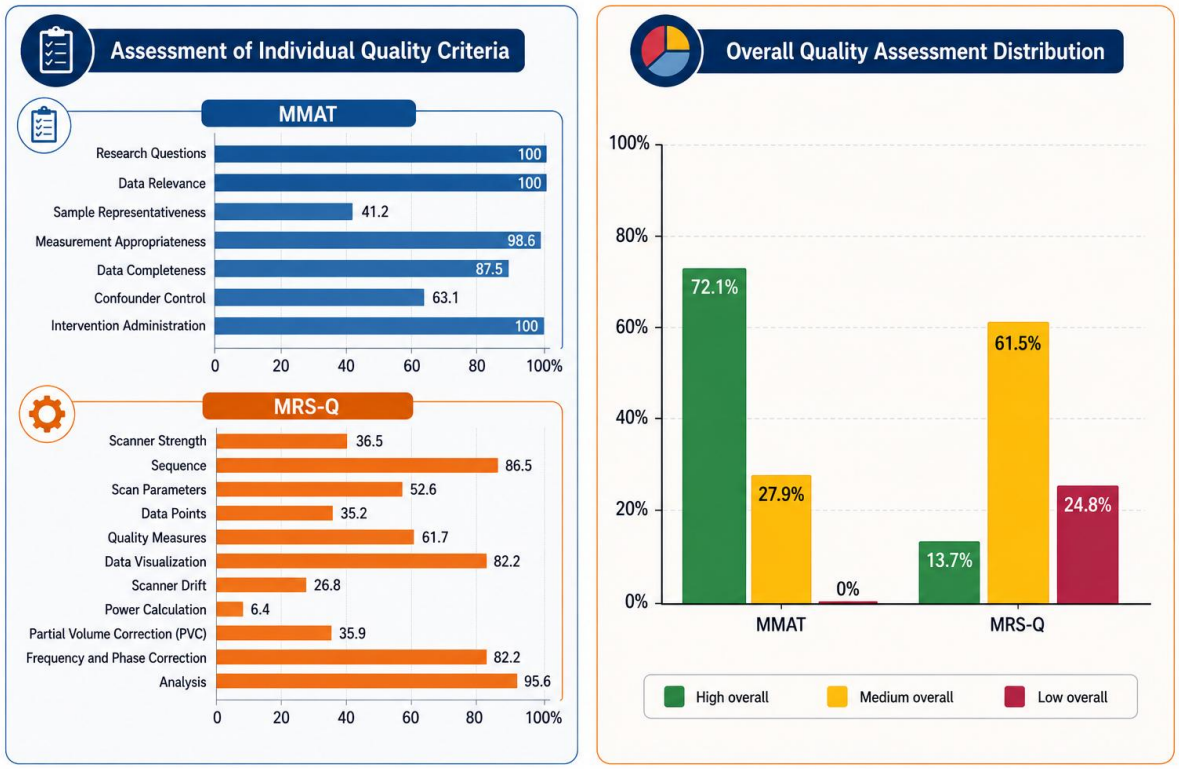


Figure 4. Methodological quality assessment of the included studies. The left panel depicts the percentage of the included studies rated positive for each quality item according to MMAT and MRS-Q criteria. MMAT criteria evaluate overall methodological quality, while MRS-Q criteria relate to adherence to spectroscopy acquisition, processing, analysis and reporting. In turn, the right panel presents the aggregated quality scores of the included studies according to the MMAT and MRS-Q. Abbreviations: MMAT: Mixed Methods Appraisal Tool; MRS-Q: The Magnetic Resonance Spectroscopy Quality Tool

3.5 ^{1}H MRS studies

Among the 272 ^{1}H-MRS articles included, the studies were organized according to the primary epileptic population and application area addressed by the research. Two hundred seventeen articles explored ^{1}H-MRS in focal epilepsy, 25 articles explored ^{1}H-MRS in generalized epilepsy, 19 articles explored ^{1}H-MRS in a mixed/uncharacterized epilepsy population, and 11 articles explored ^{1}H-MRS in tumor-associated epilepsy.

3.5.1 Focal epilepsy

The 217 included articles that explored focal epilepsy were distributed among four main domains according to the described clinical applications of ^{1}H-MRS: localization/diagnosis and

pathophysiology (160 studies); cognitive correlates (17 studies); treatment-related effects (27 studies); and prognosis (36 studies). The following sections present the evidence from these domains in greater detail.

3.5.1.1 Localization, diagnosis, and pathophysiology

Within the domain of localization, 160 articles reported on the diagnostic, localization-related and pathophysiological relevance of ^{1}H-MRS in focal epilepsy. Specifically, 81 of the included articles explored SVS, 70 articles explored MRSI, eight articles explored *ex vivo* studies, and one article explored whole-brain MRS. Below are the details from each of these four approaches.

3.5.1.1.1 Single-voxel spectroscopy

In 81 articles, single-voxel ¹H-MRS was explored for the diagnostic, localization, and pathophysiological assessment of focal epilepsy. Over the last three decades, its application expanded from predominantly hippocampal tNAA measurements for presurgical lateralization of Mesial Temporal Lobe Epilepsy (MTLE) to a broader range of epilepsy phenotypes, brain regions, metabolites, and clinical questions. Later studies increasingly included MRI-negative epilepsy, focal cortical dysplasia (FCD) and other malformations of cortical development (MCDs), autoimmune and extratemporal epilepsies, pediatric populations, and post-surgical and postictal assessments, alongside investigation of metabolites beyond tNAA, including tCr, tCho, mI, and Glx.

Despite substantial methodological and clinical heterogeneity, 49 of the 81 studies reported decreased tNAA measures in or around the epileptogenic region across MTLE, FCD, MCD, acquired focal epilepsies, and MRI-negative TLE. These reductions were demonstrated using absolute quantification as well as tNAA/tCr, tNAA/tCho, and tNAA/(tCho + tCr) ratios.

Reduced tNAA was historically interpreted primarily as a marker of neuronal loss/dysfunction, particularly in MTLE-HS, where marked hippocampal reductions were repeatedly demonstrated and, in histopathological studies, were associated with neuronal loss and gliosis[33–38]. However, reduced tNAA was also demonstrated in focal epilepsies without hippocampal sclerosis, including MRI-negative TLE, neocortical epilepsy, FCD, and other MCDs[39–51] . Together, these findings indicate that reduced tNAA is not specific to irreversible neuronal loss and may also reflect neuronal metabolic dysfunction in structurally preserved or non-sclerotic epileptogenic tissue. The regional distribution of these and other metabolic abnormalities across the included SVS studies is summarized in Table 1 and Figure 5. Given the relatively large voxel sizes used in SVS, measurements attributed to cortical regions may also include contributions from underlying white matter and should not be interpreted as exclusively cortical.

Table 1. Evidence of regional metabolite alterations using the 81 included SVS ^{1}H-MRS articles in the domain of focal epilepsy. Abbreviations: tNAA: total N-acetylaspartate; NAA: N-acetylaspartate; tCr: total creatine; Cr: creatine; tCho: total choline; Cho: choline; mI: myo-inositol; Glu: glutamate; Gln: glutamine; Glx: glutamate plus glutamine; GABA: γ-aminobutyric acid; GABA+: γ-aminobutyric acid plus co-edited macromolecules; GSH: glutathione.

Region	Metabolite	Decreased (n)	Increased (n)	Unchanged (n)	Mixed (n)	Total study-region observations	% decreased among studies	Predominant direction
Hippocampus	tNAA/NAA	21	0	1	26	48	95.5	Mixed
	tCr/Cr	15	0	1	19	35	93.8	Mixed
	tCho/Cho	13	7	1	16	37	61.9	Mixed
	mI	1	0	0	3	4	100	Mixed
	Glu	5	3	0	4	12	62.5	↓
	Gln	5	2	0	0	7	71.4	↓
	Glx	4	2	0	1	7	66.7	↓
	GABA/GABA+	1	0	0	2	3	100	Mixed
	Lactate	1	3	0	1	5	25	↑
	Lipids	1	0	0	1	2	100	↓
Mesial temporal lobe	tNAA/NAA	19	1	0	5	25	95	↓
	tCr/Cr	10	1	1	4	16	83.3	↓
	tCho/Cho	8	3	1	2	14	66.7	↓
	mI	2	0	0	2	4	100	↓
	Glu	2	2	0	1	5	50	↓
	Glx	0	0	0	3	3	0	Mixed
	Lactate	2	0	0	0	2	100	↓
Temporal neocortex	tNAA/NAA	6	2	0	1	9	75	↓
	tCr/Cr	5	0	0	0	5	100	↓
	tCho/Cho	4	2	0	1	7	66.7	↓
	mI	2	1	0	0	3	66.7	↓
Temporal pole	tNAA/NAA	2	0	0	2	4	100	↓
	tCr/Cr	1	0	0	3	4	100	Mixed
	tCho/Cho	2	0	0	2	4	100	↓
Insula	tNAA/NAA	2	0	1	1	4	66.7	↓
	tCr/Cr	0	0	1	2	3	0	Mixed
Frontal cortex	tNAA/NAA	10	1	0	6	17	90.9	↓
	tCr/Cr	4	2	1	1	8	57.1	↓
	tCho/Cho	4	2	1	1	8	57.1	↓
	mI	3	0	0	6	9	100	Mixed
	Glu	1	3	0	1	5	25	↑
	Gln	1	4	0	0	5	20	↑
	Glx	2	3	1	3	9	33.3	↑
	GABA/GABA+	1	0	0	2	3	100	Mixed
	GSH	2	0	0	0	2	100	↓
	tNAA/NAA	4	0	0	0	4	100	↓
	tCr/Cr	3	0	0	0	3	100	↓

	tCho/Cho	2	0	0	0	2	100	↓
	GSH	0	0	0	3	3	0	Mixed
Occipital cortex	tNAA/NAA	2	0	0	2	4	100	↓
	tCr/Cr	0	1	0	2	3	0	Mixed
	tCho/Cho	1	1	0	1	3	50	↓
	Glx	0	0	0	2	2	0	Mixed
	GABA/GABA+	1	1	0	0	2	50	↓
Cingulate cortex	tNAA/NAA	1	0	0	1	2	100	↓
	tCr/Cr	1	0	0	1	2	100	↓
	tCho/Cho	1	0	1	0	2	50	↓
	mI	1	0	1	0	2	50	↓
Thalamus	tNAA/NAA	3	0	0	1	4	100	↓
	tCr/Cr	2	0	1	0	3	66.7	↓
	tCho/Cho	3	0	1	0	4	75	↓
	mI	1	0	1	0	2	50	↓
	Glx	0	2	0	0	2	0	↑
Cerebellum	tNAA/NAA	1	0	0	1	2	100	↓
	tCr/Cr	1	5	0	0	6	16.7	↑
	tCho/Cho	1	5	0	0	6	16.7	↑
Whole brain / multiregional	tNAA/NAA	2	0	0	1	3	100	↓
	tCr/Cr	1	0	0	2	3	100	Mixed
	tCho/Cho	1	0	0	1	2	100	↓

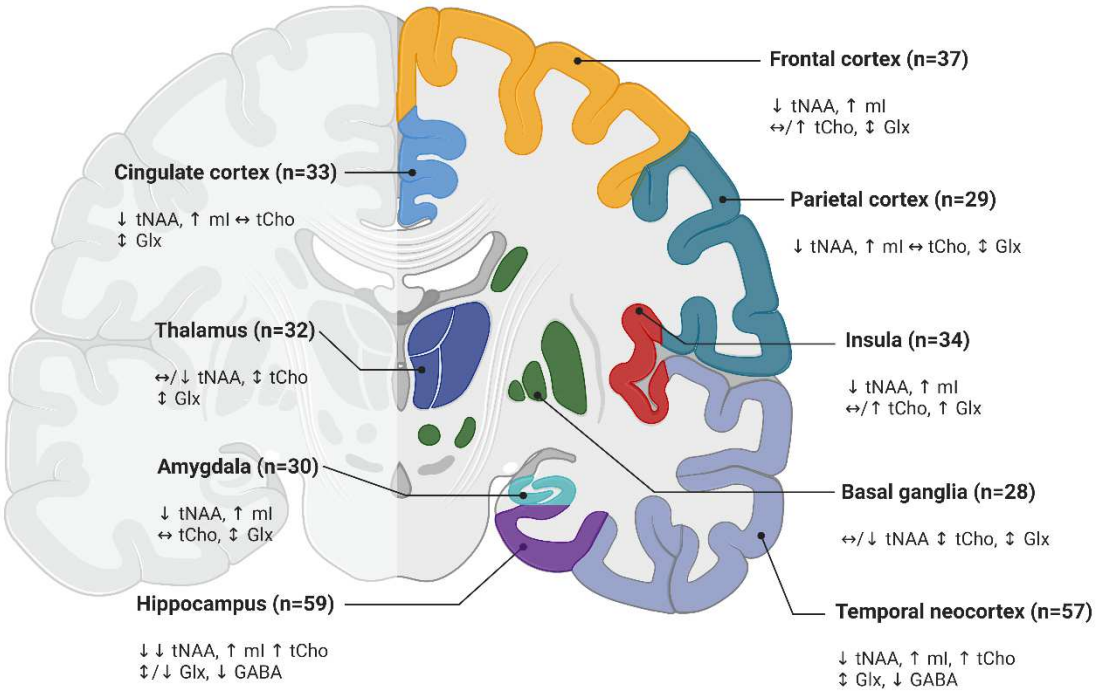


Figure 5. Whole-brain metabolic atlas summarizing regional metabolic abnormalities identified by SVS in focal epilepsy. Abbreviations: tNAA: total N-acetylaspartate; mI: myo-

inositol; tCho: total choline; Glx: glutamate plus glutamine; GABA: γ-aminobutyric acid; tCr: total creatine; Glu: glutamate; Gln: glutamine. Created in BioRender. Rahnemayan, S. (2026) https://BioRender.com/nl83z8t

A major conceptual contribution of the SVS literature was the demonstration that metabolic abnormalities are not confined to the epileptogenic region. Beyond the hippocampus and mesial temporal structures, abnormalities were identified bilaterally and in the temporal neocortex, frontal cortex, insula, thalamus, cingulate, parietal, and occipital cortices, with their extent in some studies related to seizure burden, disease duration, structural abnormalities, interictal activity, or clinical outcome[34,38,41,43,46,49,50,52–56]. Although bilateral abnormalities could complicate lateralization by reducing hemispheric asymmetry, these findings increasingly supported focal epilepsy as a distributed network disorder with metabolic consequences extending beyond the epileptogenic focus[41,46,49,54,55,57].

SVS also frequently identified abnormalities beyond those visible on conventional structural MRI. Reduced hippocampal tNAA was demonstrated in MRI-negative epilepsy, although generally less pronounced than in MRI-positive TLE with hippocampal sclerosis, while metabolic abnormalities could also extend beyond MRI-visible lesions in HS, FCD, and other MCDs[39,43,46–48,50,58,59]. SVS, therefore, provided information complementary to structural MRI and, in some studies, ^{18}F-FDG-PET, particularly when conventional imaging was negative or equivocal[39,43,51,53,58–61].

Other metabolites provided complementary but less consistent information. Alterations in tCr and tCho varied across epilepsy syndromes and anatomical regions, indicating that neither can be assumed to be an invariant reference for ratio-based quantification, while mI showed region- and pathology-dependent increases or decreases consistent with heterogeneous glial and osmotic alterations[38,41,43,48,50,57,62]. Higher magnetic field and edited spectroscopy increasingly improved assessment of Glu, Gln, and GABA; however, glutamatergic measures showed heterogeneous, pathology-, region-, and state-dependent increases or decreases rather than a universal pattern of alterations[41,43,48–50,57,63,64]. Finally, lactate and lipid presence were primarily associated with acute ictal or early postictal metabolic stress and could disappear during seizure-free follow-up[65].

3.5.1.1.2 Magnetic resonance spectroscopic imaging

Seventy studies used ^{1}H-MRSI to investigate focal epilepsy for diagnostic, localization, and pathophysiological purposes. Most focused on TLE, particularly MTLE-HS, although MRI-negative epilepsy, frontal and other extratemporal epilepsies, FCD, and other MCDs were also investigated. Technical approaches evolved from two-dimensional acquisitions at 1.5T to high-field, short-echo, volumetric, and whole-brain methods.

Across studies, metabolic abnormalities showed a broadly hierarchical spatial distribution, being greatest in the epileptogenic core and progressively less pronounced in ipsilateral propagation or perilesional regions, contralateral homologous areas, and remote cortical and subcortical networks (Figure 6). The epileptogenic core showed the most consistent abnormalities, particularly in HS-associated MTLE, although metabolic alterations were also demonstrated in neocortical lesions, FCD, other MCDs, and MRI-negative epilepsy[5,7,9,10,12,15,16,22,66–70].

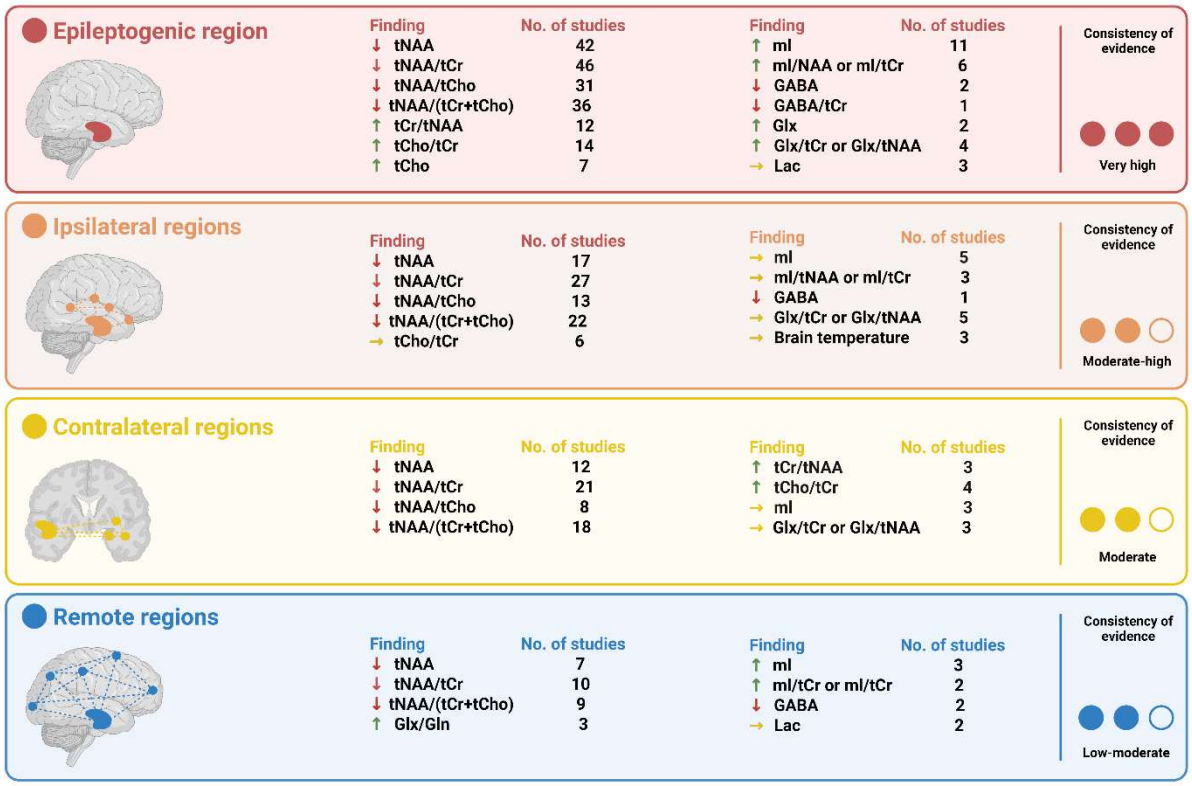


Figure 6. Hierarchical spatial distribution of metabolic abnormalities in focal epilepsy detected by ^{1}H-MRSI. Spatial categories were defined according to anatomical location relative to the presumed or independently established epileptogenic region: core, within the epileptogenic region; ipsilateral extra-core, regions outside the core in the same hemisphere; contralateral, regions in the opposite hemisphere; and remote, anatomically distant extrafocal regions. These categories describe the spatial distribution of reported abnormalities and do not necessarily imply demonstrated network connectivity. Abbreviations: NAA: N-acetylaspartate; tNAA: total N-acetylaspartate; Cho: choline-containing compounds; tCho: total choline; Cr: creatine; tCr: total creatine; mI: myo-inositol; Glx: glutamate plus glutamine; Gln: glutamine; GABA: γ-aminobutyric acid. Created in BioRender. Rahnemayan, S. (2026) https://BioRender.com/nl83z8t

Reduced tNAA, measured as absolute concentrations or tNAA-based ratios, was the dominant and most consistent metabolic finding. Reductions were generally strongest within the

epileptogenic region but frequently extended into ipsilateral temporal and perilesional structures and contralateral homologous regions, while more remote abnormalities involved frontal and cingulate cortices, thalamus, basal ganglia, parietal cortex, and occipital cortex[9,12,15,22,49,67,68,71–77]. tNAA reductions in structurally normal tissue and postoperative normalization of contralateral abnormalities suggest that reduced tNAA may reflect both irreversible neuronal loss and potentially reversible metabolic dysfunction[11,75,78,79].

In contrast, tCr, tCho, and mI showed heterogeneous increases, decreases, or no significant changes depending on pathology, anatomical region, and methodology. Glu-, Gln-, Glx-, and GABA-related findings were similarly variable, while lactate abnormalities were mainly reported in peri- or postictal settings and recent spectroscopic thermometry studies identified focal or bilateral temperature elevations associated with acute tissue and inflammatory changes[10,16,49,67,77,80–86].

From a clinical localization perspective, reported lateralization performance ranged from approximately 60% to 100%, with the best results generally achieved in unilateral TLE and when MRSI was combined with structural MRI or hippocampal volumetry[5–7,12,15,55,66,72,75,77,81,87–97]. Larger-volume or whole-temporal acquisitions generally performed better than hippocampal sampling alone in retrospectively identifying maximal metabolic abnormalities[12,15,22,55,66,71,72,75,76,88,98].

Despite the common tNAA reduction, metabolic patterns differed across focal epilepsy phenotypes (Figure 7). HS-associated MTLE showed the most stereotypical pattern, with marked ipsilateral hippocampal tNAA reduction and frequent extension into ipsilateral temporal and extrahippocampal structures and contralateral mesial temporal regions. MRI-negative TLE generally showed smaller, less consistently lateralized, and more heterogeneous abnormalities, while frontal and other extratemporal epilepsies, FCD, and other MCDs showed broader lesion, perilesional, and network-level alterations[5,9,12,15,16,22,66,67,69–71,73,99,100].

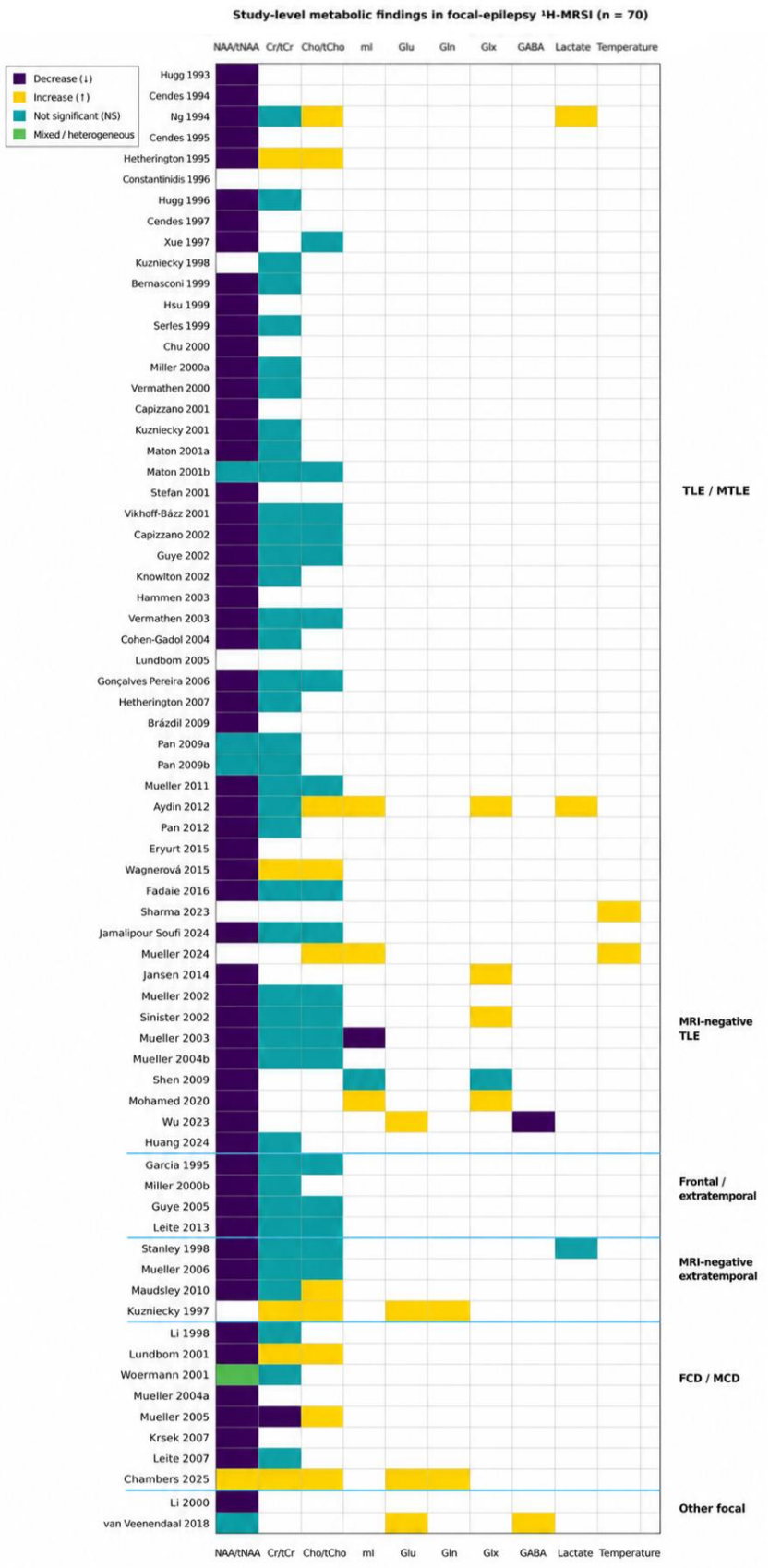


Figure 7. Metabolic heatmap of studies, grouped by epilepsy phenotype. Abbreviations: ^{1}H-MRSI: proton magnetic resonance spectroscopic imaging; TLE: temporal lobe epilepsy;

MTLE: mesial temporal lobe epilepsy; FCD: focal cortical dysplasia; MCD: malformation of cortical development; MRI: magnetic resonance imaging; NAA: N-acetylaspartate; tNAA: total N-acetylaspartate; Cr: creatine; tCr: total creatine; Cho: choline; tCho: total choline; mI: myo-inositol; Glu: glutamate; Gln: glutamine; Glx: glutamate plus glutamine; GABA: γ-aminobutyric acid; NS: not significant.

Symmetrical and bilateral abnormalities were frequent, particularly in chronic epilepsy, supporting distributed network dysfunction rather than necessarily indicating independent bilateral epileptogenic zones (EZ). MRSI was also particularly valuable in MRI-negative epilepsy, where metabolically abnormal tissue could be detected despite negative structural MRI. Nevertheless, specificity for delineating the seizure-onset zone (SOZ) remained variable, likely reflecting both the distributed nature of metabolic abnormalities and methodological limitations, such as small sample sizes and limited SNR. Consequently, comprehensive localization generally required multimodal assessment that incorporated structural MRI, video-EEG, PET, and/or invasive recordings[15,16,49,70,75,77,81,95,99,101].

3.5.1.1.3 *Ex vivo*

Eight published *ex vivo* ^{1}H-MRS studies were performed in patients with focal epilepsy between 1989 and 2017[102–109]. The majority of them explored surgically resected mesial temporal lobe tissues from patients with pharmacoresistant epilepsy[102,104,106–108]. A few studies included non-temporal tissues to assess epileptogenic metabolic fingerprints in different epilepsy populations[105,109] (Table 2).

Decreased levels of tNAA were consistently reported in hippocampal sclerosis, mesial temporal lobe epilepsy, as well as in the temporal cortex, and the epileptogenic neocortex, pointing to a 3 dysfunction (Sama, what is this—a “3 dysfunction” ?) of neurons[102,104–108]. Reduced tNAA was frequently associated with neuronal loss but not consistently across different histology[102,105–108]. In contrast to tNAA, tCr and mI showed less consistent alterations across studies[102,104–107]. However, there was a large inter-study variability in the measurements of these metabolites, and no specific association with histological findings was reported[104–107].

Several of the included studies also reported on an alteration of the energy metabolism and neurotransmission in surgically resected tissues from patients with pharmacoresistant focal epilepsy[102,104–109]. Accumulation of lactate was repeatedly found in hippocampal sclerosis and the epileptogenic cortex[102,104,105,108]. An increase of Glu was also commonly found in epileptic tissues, though with no consistent association with neuronal loss or gliosis[102,104,106]. In some studies, decreased GABA, increased glucose, and succinate levels were found specific to certain pathological subgroups[105,108].

Finally, the *ex vivo* nature of the included studies allowed assessing the concentrations of a large panel of metabolites[102–109]. In particular, a multimetabolite profile involving lactate, Cho-containing compounds, Cr/phosphocreatine (PCr), N-Acetylaspartylglutamate (NAAG), and mI discriminated high- and low-spiking cortical areas in one multimodal study[109]. Thus, *ex vivo* 1H-MRS consistently showed decreased neuronal metabolites and abnormalities of energy metabolism, neurotransmission, and glial metabolism[102,104–109].

Table 2. Main findings of *ex vivo* ^{1}H-MRS studies in focal epilepsy patients. Abbreviations: Cho: choline; PCh: phosphocholine; PE: phosphoethanolamine; Cr: creatine; PCr: phosphocreatine; NAAG: N-acetylaspartylglutamate; GPC: glycerophosphocholine; NAA: N-acetylaspartate; Glu: glutamate; GABA: γ-aminobutyric acid; MTLE: mesial temporal lobe epilepsy; AHS: Ammon's horn sclerosis; CA1: cornu ammonis 1; CA3: cornu ammonis 3; DG: dentate gyrus; PHG: parahippocampal gyrus; mI: myo-inositol; Gln: glutamine; MCD: malformation of cortical development; TSC: tuberous sclerosis complex; AUC: area under the curve.

Study	Population	Resected tissue	Histopathology / Comparison	Main metabolic findings	Correlation with pathology / clinical features
Wu, 2017	Pediatric drug-resistant focal epilepsy (epileptic vs non-epileptic cortex from same patient)	Neocortex	High- *vs* low-spiking cortex	↓ Lactate, ↓ Cho, ↓ PCh, ↓ PE; multivariate ↑ Cr+PCr, ↑ NAAG, ↑ GPC; NAA, Glu and GABA unchanged	Multimetabolite profile discriminated highly epileptogenic cortex (AUC ≈0.88–0.90)
Vielhaber, 2008	MTLE (AHS *vs* lesion-related MTLE)	Hippocampal subfields (CA1, CA3, DG, PHG)	Ammon's horn sclerosis vs lesion-caused MTLE	↓ tNAA and ↑ lactate/succinate confined to CA3; ipsilateral hippocampus showed lower NAA	tNAA inversely correlated with lactate and succinate; findings suggest mitochondrial dysfunction rather than uniform neuronal loss
Petroff, 2003	Mesial TLE	Hippocampus	Hippocampal sclerosis	↓ tNAA; ↑ total Cr; ↑ mI	tNAA, Cr and mI showed no significant correlation with neuronal loss or gliosis; positive correlation between tNAA and Cr
Petroff, 2002	Mesial TLE	Hippocampus	Hippocampal sclerosis	↓ tNAA; ↑ Glu; GABA, Gln and aspartate unchanged	No correlation of tNAA, Glu, GABA or Gln with neuronal loss; positive correlation between tNAA and Glu
Aasly, 1999	Drug-resistant focal epilepsy	Temporal/ frontal neocortex	Gliosis, cortical dysplasia, tuberous sclerosis, controls	Gliosis: ↑ lactate only; MCD/TSC: ↓ tNAA, ↑ GABA; MCD also showed ↑ alanine, mI, glucose and lactate	GABA was not associated with antiepileptic drug treatment; metabolic profile differed according to histopathology

Petroff, 1995	Temporal lobe epilepsy	Temporal cortex	Epileptic tissue vs reference tissue	↓ tNAA; ↑ Glu and GABA; Cr relatively stable	Metabolic profile reflected combined neuronal loss and gliosis; neuronal fractions enriched in NAA/Glu, glial fractions in lactate/Gln/mI
Peeling, 1992	Epilepsy and brain tumors	Temporal cortex	Epileptic cortex vs tumors	Epileptic cortex contained higher tNAA, GABA, Glu, Cr and mI than tumors	Demonstrated distinct metabolic signatures between epileptic cortex and neoplastic tissue
Petroff, 1989	Epilepsy surgery specimens	Temporal cortex, frontal cortex, white matter	Regional tissue comparison	Cortex contained higher tNAA, Cr, GABA and Glu than white matter; white matter contained higher acetate and Cho	No significant differences between pathological subgroups; primarily characterized normal regional metabolic distribution

3.5.1.1.4 Whole-brain non-localized MRS

Only one study used whole-brain 1H-MRS. Kirov et al. compared ^{1}H-MRS data from patients with focal epilepsy and healthy controls. They found a decrease of whole-brain tNAA concentration by approximately 12%, whereas tCr and tCho remained unaffected. Because the tNAA decrement was found without signs of brain atrophy, it may be concluded that focal epilepsy leads to a functional impairment beyond the lesion[110].

3.5.1.2 Cognitive correlates

Seventeen studies assessed cognitive or affective performance in relation to ^{1}H-MRS abnormalities in focal epilepsy (Fig. 8). Most evidence concerned memory, particularly in temporal lobe epilepsy with mesial temporal involvement[111–121]. Across studies, poorer memory was associated with hippocampal abnormalities in several tNAA-containing ratios, including tNAA/(tCho+tCr), tCr/tNAA, tNAA/tCho, tNAA/(Cr+PCr), and tNAA/tCr. These relationships were frequently lateralized: left or dominant hippocampal dysfunction was predominantly associated with poorer verbal memory or retention, whereas right-sided abnormalities were more closely related to visual or nonverbal memory. Recognition memory was also related to tNAA/(Cr+PCr) asymmetry[114], and increasing left hippocampal tCr/tNAA showed a nonlinear relationship with poorer verbal retention[117].

Language findings showed a similar regional pattern. Higher left hippocampal tCr/tNAA was associated with poorer confrontation naming[113,116], while higher hippocampal tCho was associated with poorer language performance[122]. Beyond the hippocampus, lower tNAA and tCho in the right inferior frontal gyrus, with tNAA also related to social-communication abnormalities[123]. (Sama, this previous sentence does not make sense…) Thus, language-related metabolic associations involved both mesial temporal and frontal regions.

Processing speed and broader cognitive impairment extended these findings to other metabolites and regions. Lower parieto-occipital Glu, but not GABA+, was associated with

slower information processing[124], while higher hippocampal tCho and mI were associated with poorer processing speed[122]. Broader cognitive impairment was accompanied by lower hippocampal GABA/tCr and right hippocampal tNAA/(tCho+tCr), as well as lower anterior cingulate GABA/tCr[125]. More recently, hippocampal tCr, tCho, and M-Ins showed associations across attention, processing speed, language, learning, and memory domains[122].

Affective symptoms were likewise related to metabolic abnormalities, with greater hippocampal tCr/tNAA abnormality associated with more severe depressive symptoms[126], and temporofrontal tCho/tCr and tCr abnormalities reported in relation to depression in TLE[127]. Overall, the most consistent cognitive finding was the association between hippocampal metabolic dysfunction and memory, particularly its material-specific lateralization according to the type of memory. However, associations with language, processing speed, broader cognition, and mood involved frontal, cingulate, temporal, and parieto-occipital regions and a wider range of metabolites, including Glu, GABA, tCr, tCho, and M-Ins, supporting a distributed metabolic-network involvement in focal epilepsy.

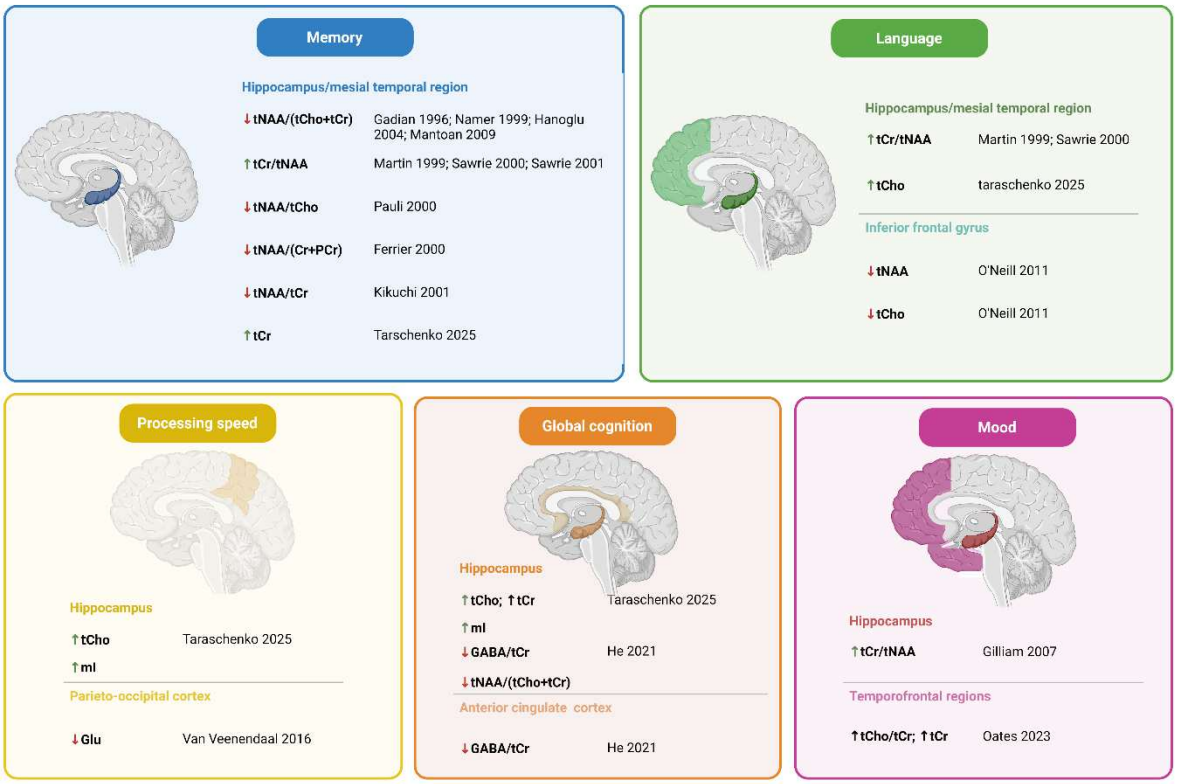


Figure 8. Regional neurochemical correlates of cognitive dysfunction identified by proton magnetic resonance spectroscopy (^{1}H-MRS) in focal epilepsy. Abbreviations: tNAA: total N-acetylaspartate; tCr: total creatine; tCho: total choline; Glx: glutamate plus glutamine; mI: myo-inositol; GABA: γ-aminobutyric acid; Glu: glutamate; Gln: glutamine; GSH: glutathione. Created in BioRender. Rahnemayan, S. (2026) https://BioRender.com/nl83z8t

3.5.1.3 Treatment-related changes

Twenty-seven studies assessed treatment-related metabolic changes in focal epilepsy with regard to ^{1}H-MRS (anti-seizure medication, epilepsy surgery, radiosurgery, neurostimulation, ketogenic diet, cannabidiol; Figure 9). Most of these studies were longitudinal with comparisons of baseline and follow-up data or treatment responder *vs* non-responder analyses[11,13,14,128–146].

An overall consistent finding across pharmacological studies was an increase in GABA-containing metabolites after vigabatrin, topiramate, or gabapentin, with most studies measuring these changes in the occipital cortex and some vigabatrin studies also assessing f regions near to the seizure onset zone [128–132,134–136,139,147–149]. Vigabatrin caused rapid and sustained elevations of GABA, together with increases in homocarnosine and 2-pyrrolidinone[128,130–132,135,139,147,148]. Similar increases in GABA, homocarnosine, and 2-pyrrolidinone were reported with topiramate[136,149]. On the other hand, valproate tended to increase Gln without consistent changes of GABA[150]. Levetiracetam increased GABA/tCr primarily in treatment responders[143]. Several studies also found that responders to vigabatrin had lower baseline levels of certain GABA-containing metabolites and larger treatment-induced increases of these compared to non-responders, providing tentative evidence for biomarker-guided treatment selection[128,130,135,139].

While pharmacological interventions primarily influenced inhibitory neurotransmission, surgical treatments mainly led to normalization of neuronal metabolism[11,13,14,137,140,142]. Temporal lobe epilepsy surgeries were largely successful in restoring tNAA and tNAA-containing metabolite ratios in patients with post-surgical seizure freedom compared to those with persistent seizures[11,13,14,137,140,142]. Gamma knife radiosurgery, in turn, produced dynamic metabolic changes, including reductions in NAA and other metabolites, transient alterations in Cho and lipid signals, and subsequent partial metabolic recovery[138,141].

Changes of glutamatergic metabolism were more inconsistent across different treatments[124,142,144,150]. For example, anti-seizure medications associated with cognitive side effects tended to decrease Glu levels[124], whereas cathodal transcranial direct current stimulation increased Glx levels and glutathione and decreased GABA and the GABA/Glx ratio, thus modulating the excitatory-inhibitory balance[144]. A modified Atkins/ketogenic diet increased glutathione and GSH/tCr without significant changes of tNAA or ketone bodies[145]. Finally, cannabidiol decreased MRSI-estimated brain temperature within the SOZ, suggesting a potential reduction in neuroinflammatory activity[146].

Thus, treatment-related changes identified in ^{1}H-MRS studies of focal epilepsy mainly reflect response to treatment with GABAergic anti-seizure medications and seizure freedom after

epilepsy surgery with subsequent normalization of tNAA. Inconsistencies in findings for glutamatergic, oxidative stress-related, ketone body metabolism, and brain temperature suggest that these reflect more treatment-specific phenomena.

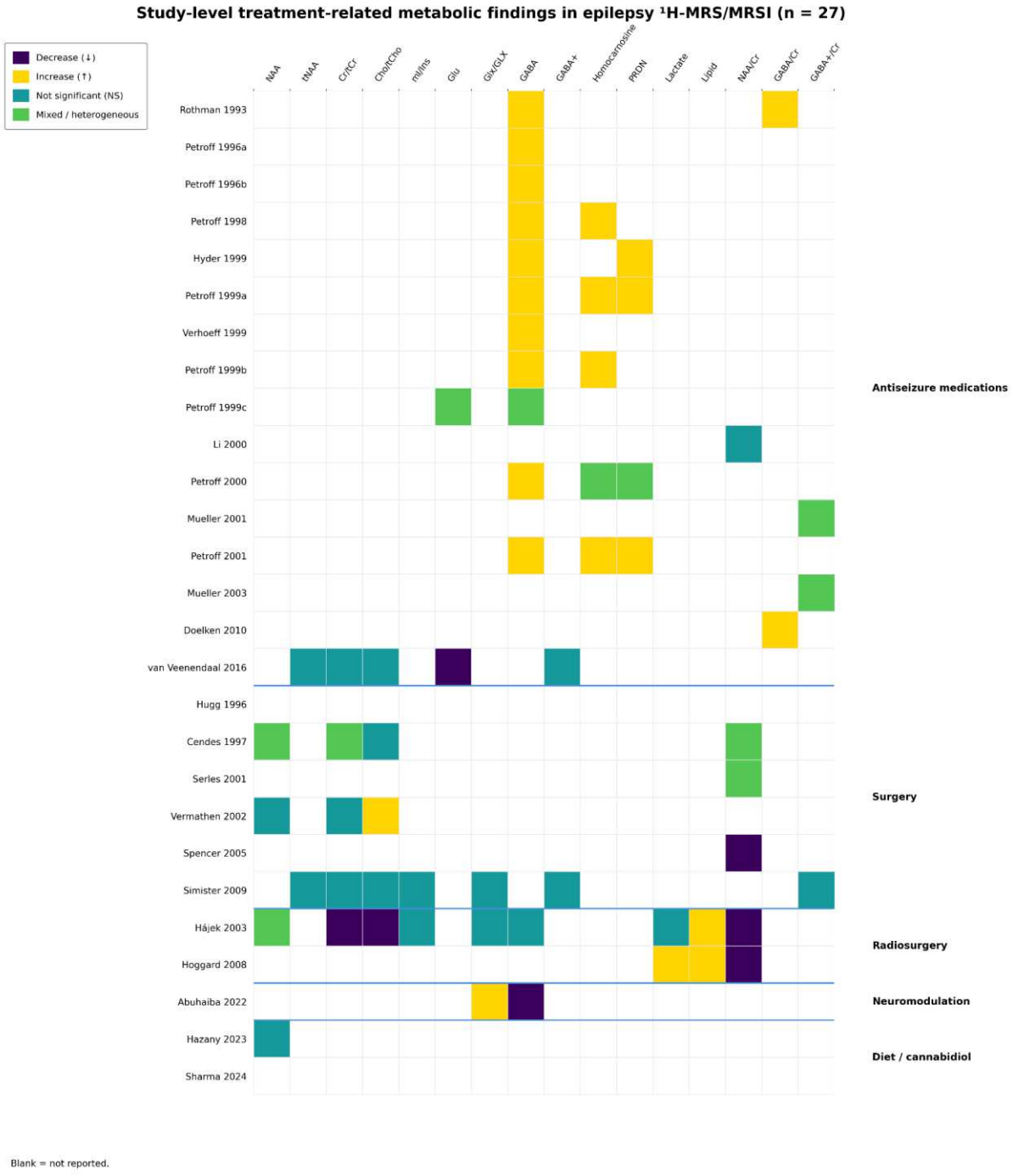


Figure 9. Summary of treatment-related metabolic alterations reported by the 27 included ¹H-MRS studies in focal epilepsy. Abbreviations: NAA: N-acetylaspartate; NAAt: total N-acetylaspartate; Cr: creatine; tCr: total creatine; Cho: choline; tCho: total choline; mI: myo-inositol; Ins: inositol; Glu: glutamate; Glx: glutamate plus glutamine; GLX: glutamate plus glutamine; GABA: γ-aminobutyric acid; GABA+: γ-aminobutyric acid plus co-edited

macromolecules; PCr: phosphocreatine; PDRN: 2-pyrrolidinone; SF: seizure-free; PS: persistent seizures; NS: not significant; R: responder; non-R: non-responder; EZ: epileptogenic zone; tDCS: transcranial direct current stimulation; AUC: area under the curve; BL: baseline.

3.5.1.4 Prognostic biomarkers

Thirty-six studies assessed the predictive value of ^{1}H-MRS in focal epilepsy. Most focused on surgical outcome and postoperative metabolic recovery[13,14,140,151–161], while others investigated pharmacological response or resistance[56,135,139,162–165], epilepsy severity and seizure burden[112,166–170], cognitive outcome[112,120], and seizure recurrence after a first seizure[171] (Figure 10 and Table 3).

Table 3. Prognostic applications of ^{1}H-MRS in focal epilepsy. Abbreviations: MRS: magnetic resonance spectroscopy; NAA: N-acetylaspartate; Cr: creatine; GABA: γ-aminobutyric acid; Glu: glutamate; tCr: total creatine; mI: myo-inositol.

Prognostic domain	Main MRS pattern	Prognostic interpretation	Supporting studies
Postoperative seizure outcome	Focal/asymmetric ↓NAA; preserved contralateral metabolism; concordance between metabolic abnormality and resection	Greater likelihood of postoperative seizure freedom	Ende 1997; Cendes 1997; Li 2000; Eberhardt 2000; Feichtinger 2001; Stefan 2001; Antel 2002; Kantarci 2002; Lee 2005; Spencer 2005; Chernov 2009; Pan 2013; Pan 2021
Poor postoperative outcome and distributed disease	Bilateral or extensive ↓NAA-based ratios; unresected metabolic abnormalities	Persistent seizures and broader epileptic-network involvement	Ende 1997; Cendes 1997; Li 2000; Eberhardt 2000; Stefan 2001; Lee 2005; Spencer 2005; Chernov 2009; Pan 2013; Pan 2021
Postoperative metabolic recovery	Postoperative recovery of NAA/Cr in residual ipsilateral or contralateral tissue	Reversible neuronal dysfunction after successful seizure control	Cendes 1997; Serles 2001; Hanoglu 2004; Spencer 2005; Lantz 2006
Disease severity and seizure burden	↓NAA or NAA ratios; ↓GABA; ↑Cr; broader metabolic involvement	Greater seizure activity, interictal burden, chronic dysfunction or inflammatory injury	Petroff 1996; Garcia 1997; Mendes-Ribeiro 1998; Tasch 1999; Namer 1999; Burneo 2004; Hammen 2007; Briellmann 2007; Wang 2024
Pharmacoresistance and medication response	Bilateral ↓NAA/Cr; ↓Glu/tCr; ↑mI/tCr; baseline and treatment-related GABA changes	Identification of drug resistance or treatment responsiveness	Mueller 2001; Mueller 2003; Campos 2010; Pimentel-Silva 2020; Abo El-Kasem 2025; Zhang 2026
Cognitive prognosis	Bilateral hippocampal metabolic reserve and asymmetry	Risk of postoperative verbal or visual memory decline	Namer 1999; Hanoglu 2004
Seizure recurrence and epileptogenesis	Combined hippocampal MRS, structural and diffusion abnormalities	Potential identification of recurrence after a first seizure	Schmidt 2021
Presurgical localization supporting prognosis	Ipsilateral ↓NAA-based ratios, lactate or regional metabolic asymmetry	More confident localization and selection of resection target	Ende 1997; Knowlton 1997; Vikhoff-Baaz 2001; Kantarci 2002; Gonçalves Pereira 2006; Chernov 2009; Pan 2013; Pan 2021; Abo El-Kasem 2025

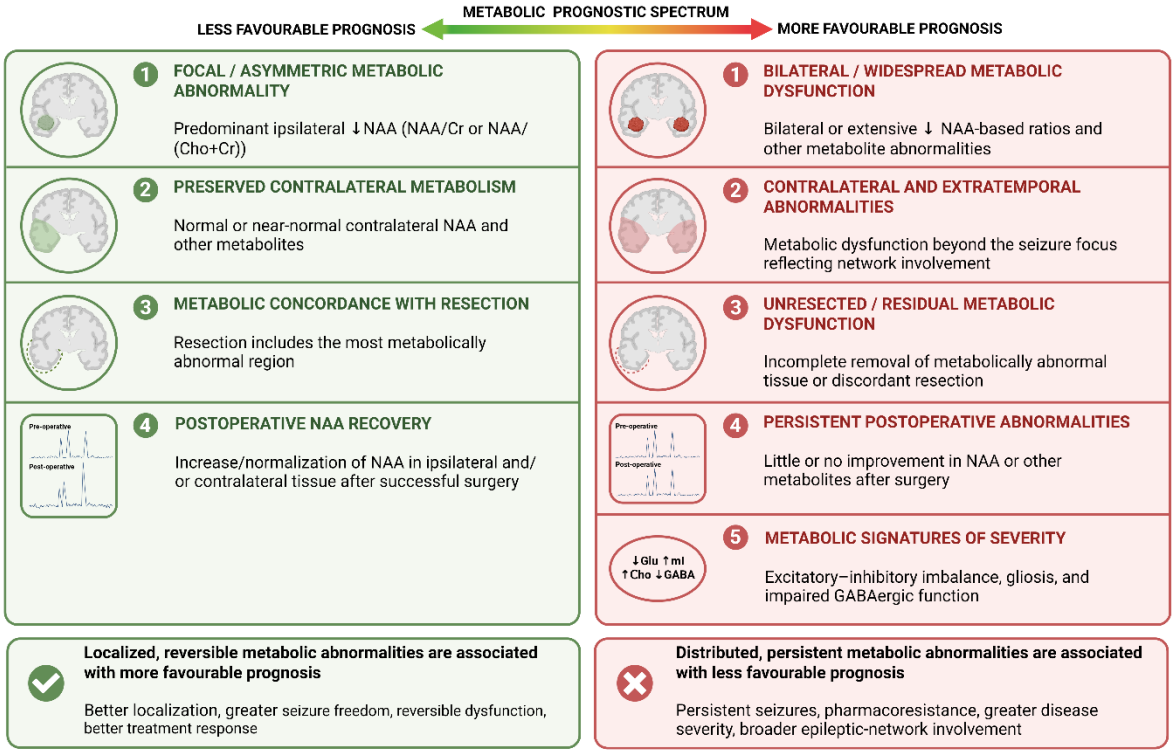


Figure 10. Prognostic metabolic patterns identified by ^{1}H-MRS in focal epilepsy. Abbreviations: NAA: N-acetylaspartate; Cr: creatine; Cho: choline; Glu: glutamate; mI: myo-inositol; GABA: γ-aminobutyric acid; Pre-op: preoperative; Post-op: postoperative. Created in BioRender. Rahnemayan, S. (2026) https://BioRender.com/nl83z8t

The strongest evidence was found for the prognostic importance of ^{1}H-MRS in epilepsy surgery[13,14,140,151–158,160,161]. Patients with unilateral decreases of tNAA or tNAA ratios concordant with the EZ were more likely to become seizure-free after temporal lobectomy, especially if the metabolically abnormal tissue was completely removed[151,153,156,157,160]. By contrast, contralateral or bilateral abnormalities and metabolic dysfunction that extended beyond the presumed EZ were more frequently associated with persistent postoperative seizures[140,152–156,158,161].

Moreover, several longitudinal studies revealed that successful epilepsy surgery was frequently associated with partial or complete normalization of tNAA levels after surgery, both in the affected and the unaffected hemisphere, while post-operative seizures were related to a lesser degree of normalization, reflecting the functional reserve of neurons in the Lantz 2006 epileptogenic region [13,14,159]. (Sama, why say the “Lantz 2006” thing? Any reason?)

Apart from the surgical outcome, MRS findings were linked to the severity of epilepsy[56,112,135,139,162–170]. Lower tNAA or tNAA ratios, decreased GABA levels, higher tCr, and broader metabolic alterations were associated with a higher number of seizures, increased inter-ictal epileptiform activity, longer duration of illness in some studies, and

pharmacoresistance[56,112,162–167,169,170]. More recent studies also indicated that the combined analysis of several metabolites, including tNAA, Glu, and mI, may be more informative than the assessment of individual substances in predicting response to anti-epileptic drugs[164,165].
The role of MRS in cognitive prognosis was less consistent across studies. Reduced bilateral hippocampal reserve was linked to a poorer verbal memory and visual memory after temporal lobectomy[112,120]. One study also demonstrated that the combination of hippocampal MRS with structural and diffusion MRI scans may predict the development of epilepsy after the first seizure, thus expanding the potential of MRS in epilepsy management[171].
In summary, most of the studies demonstrated that proton MRS is a valuable tool for seizure outcome prediction in focal epilepsy. The laterality of changes, along with the extent and reversibility of abnormalities, appears to be crucial in distinguishing seizure-free and non-seizure-free patients after temporal lobectomy. Thus, multiple metabolite measurements, including tNAA and its ratios, are strong indicators of disease severity and post-surgical recovery. Although different methods and reference values were used in the reviewed studies, limiting the comparison of the results, the overall contribution of MRS to the current understanding of focal epilepsy appears significant.

3.5.2 Generalized epilepsy

A total of 25 studies examined neurometabolism in generalized epilepsies using ^{1}H-MRS. Juvenile myoclonic epilepsy (JME) was the most common generalized epilepsy type and was followed by idiopathic/genetic generalized epilepsy (IGE/GGE), photosensitive epilepsy, absence epilepsies, and generalized tonic-clonic seizures (GTCS). The thalamus and frontal cortex were the most commonly studied brain regions, with an increased emphasis on the thalamo-cortical network (Figure 11).
The most frequently reported metabolite was tNAA, which was found to be decreased in most of the generalized epilepsies, particularly in the thalamus and frontal cortex, but also in the motor cortex, hippocampus, and cingulate regions[172–188]. Other metabolites, including tCr and tCho, showed less consistent alterations, while Glx, Glu, Gln, and GABA were variably impaired[175,176,178,180,182–186,189]. mI was decreased in a few studies[176,178,182,183,190], while lactate was reported to be elevated only in photosensitive epilepsy[191,192].
Moreover, some of the reviewed articles revealed unique patterns for each of the generalized epilepsies. The broadest range of metabolic changes was found in JME, implicating frontal, temporal, hippocampal, motor, and subcortical structures[172,173,176,179–181,183,184,188,190]. In contrast, IGE/GGE studies frequently demonstrated thalamic abnormalities[174,178,185,186,193]. GTCS were associated with decreased tNAA in the thalamus and widespread Glx abnormalities[176,178,182], while absence epilepsies were characterized by relatively isolated

decreases of thalamic tNAA[177,187]. However, photosensitive epilepsy was linked to occipital abnormalities, including elevated lactate levels and increased occipital tNAA[191,192,194]. Thus, the most consistent findings across generalized epilepsies were decreased tNAA in the thalamus and frontal lobe, supporting dysfunction within distributed thalamo-cortical networks[172–187,195].

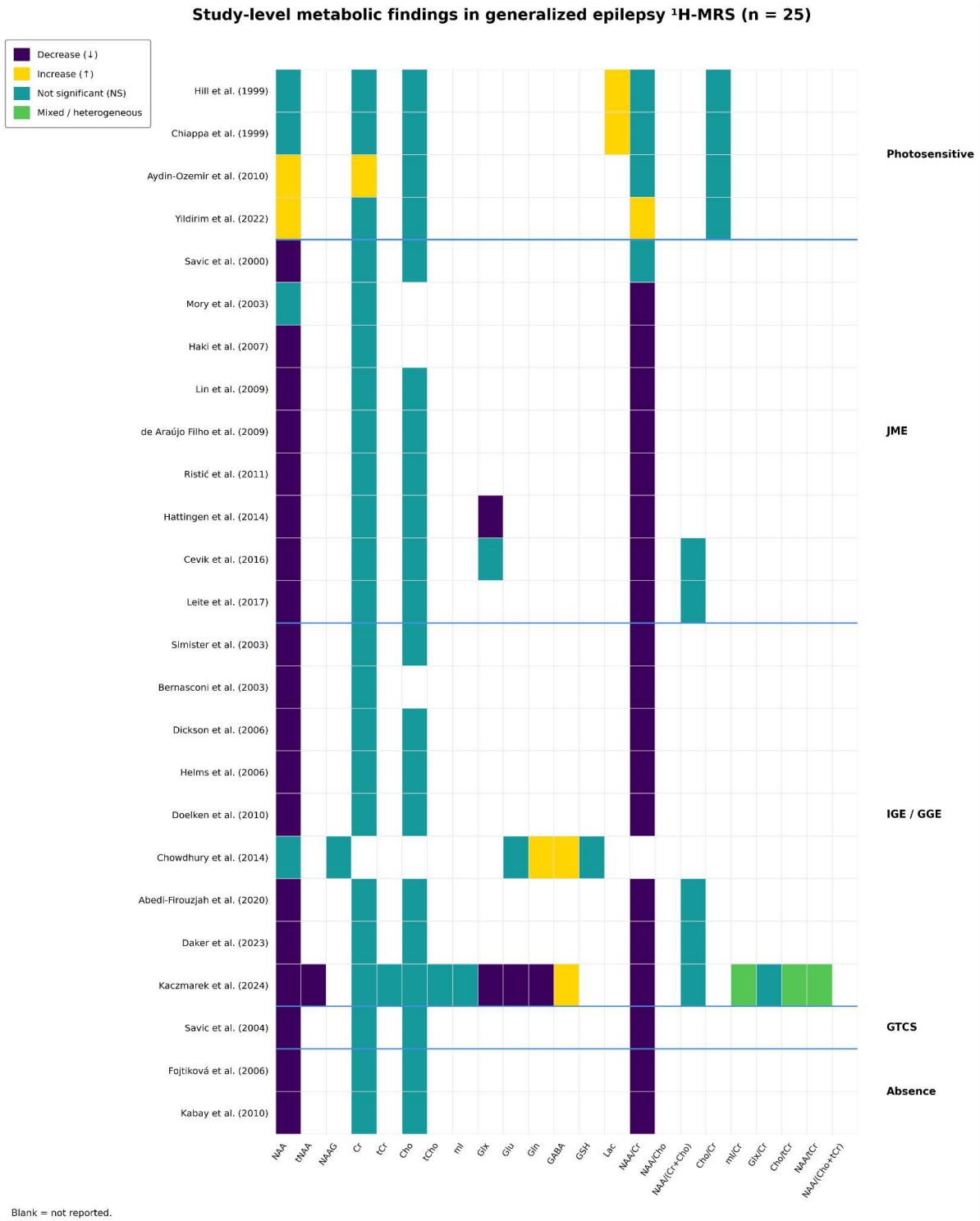


Figure 11. Heatmap summarizing metabolite alterations reported by ¹H-MRS studies in generalized epilepsy syndromes. Abbreviations: JME, juvenile myoclonic epilepsy; IGE,

idiopathic generalized epilepsy; GGE, genetic generalized epilepsy; GTCS, generalized tonic-clonic seizures; CAE, childhood absence epilepsy; JAE, juvenile absence epilepsy; ECS, eye-closure sensitivity; NAA, N-acetylaspartate; tNAA, total N-acetylaspartate; Cr, creatine; tCr, total creatine; Cho, choline-containing compounds; tCho, total choline; mI, myo-inositol; Glx, glutamate + glutamine; Glu, glutamate; Gln, glutamine; GABA, γ-aminobutyric acid; Lac, lactate.

3.5.3 Tumor-associated epilepsy

Epilepsy associated with tumors was evaluated in 11 studies, most of which were published recently and primarily focused on diffuse gliomas, including isocitrate dehydrogenase (IDH)-mutant tumors. Despite different study objectives, there was a trend for the field to transition from characterization of conventional metabolite patterns to investigation of specific features of epileptogenicity, seizure burden, and post-surgical outcomes.

Across the analyzed reports, the most common metabolite abnormalities were increases in excitatory amino acids[196–200]. In particular, elevations of Glu, Glx, or Glu-containing ratios were consistently linked to seizures, interictal epileptiform activity, post-surgical epilepsy recurrence, or treatment resistance in patients with tumor-associated epilepsy[196–200]. Recent studies reported increased Glu-, Glx-, and Glx/GABA-related measures in tumor-associated epilepsy, supporting a potential imbalance between excitatory and inhibitory metabolism[197–200].

The peritumoral area was another major finding, as increases in excitatory amino acids were often reported in both the tumor tissue and the surrounding area, with the latter showing more prominent alterations[196,197,199,200]. Thus, diffuse increases in Glu were commonly observed in patients with tumor-associated epilepsy compared to those with nonepileptic disorders, while specific areas around the tumor showed more prominent increases[196–200]. This pattern was similar to the patterns seen in focal epilepsy outside the context of tumors, highlighting the role of the peri-lesional area in the development of tumor-associated epilepsy[196,199–201]. The influence of seizures on the wider cortical network appears to be especially prominent in this population, as several reports found widespread decreases in tNAA levels in tumor-associated epilepsy[199,201].

Multiple reports directly evaluated the ability of MRS metrics to predict specific aspects of tumor-associated epilepsy[196–198,200,202,203]. In particular, increased ratios of excitatory amino acids were consistently linked to an increased risk of post-surgical epilepsy, with Glu/Cr and Glu/tCr being the most common metrics[196,197]. Similarly, elevated lactate ratios were highlighted as potential predictors of pharmacoresistance to anti-epileptic drugs[196]. Finally, *in vivo* MRS findings have recently demonstrated the potential role of 2-hydroxyglutarate in

tumor-associated epilepsy, as increased levels of this metabolite were independent predictors of seizure occurrence in patients with IDH-mutant gliomas[203].

Finally, the value of traditional neuronal and membrane metabolites was broadly inconsistent across reports[196,199,201–205]. Specifically, increases and decreases in NAA-containing metabolites were commonly reported across different tumor types, brain regions, and comparison groups[196,199,201–205]. Similarly, tCho and tCr tended to show inconsistent patterns across different studies, while their association with epilepsy was mostly limited to the comparison with non-epileptic control groups[197,199,201,203–205]. Thus, individual metabolites were only moderately informative about the presence or nature of epilepsy. In contrast, the ratio of Glu to tCr appeared to be a sensitive indicator of tumor epileptogenicity, potentially reflecting alterations of the neuronal-glial balance in this type of epilepsy[196–200] (Figure 12).

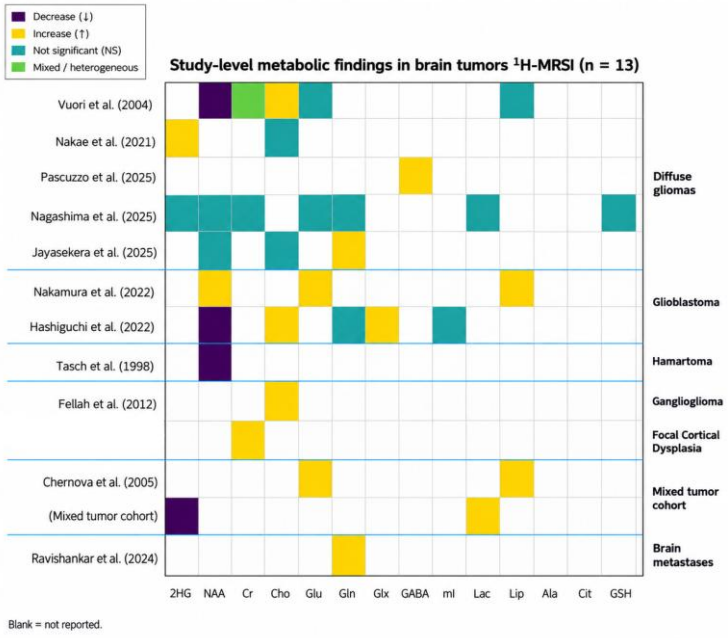


Figure 12. Summary of metabolite alterations reported in tumor-associated epilepsy studies. Abbreviations: NAA = *N*-acetylaspartate; tNAA = total *N*-acetylaspartate; Cho = choline-containing compounds; Cr = creatine; tCr = total creatine; Glu = glutamate; Glx = glutamate + glutamine; Gln = glutamine; GABA = γ-aminobutyric acid; 2HG = 2-hydroxyglutarate; GSH = glutathione; mI = myo-inositol; Lac = lactate; Lip = lipids; Ala = alanine; Cit = citrate; DNT = dysembryoplastic neuroepithelial tumor; FCD = focal cortical dysplasia; GG = ganglioglioma; GBM = glioblastoma multiforme; IDH = isocitrate dehydrogenase; IIDs = interictal epileptiform discharges.

3.5.4 Mixed epilepsy populations

Nineteen studies evaluated proton MRS in the context of heterogeneous epilepsy populations or clinical settings that did not appear to be dominated by focal or generalized epilepsy. Rather

than aiming to identify unique features of specific epilepsy syndromes, these reports investigated broader questions, such as the role of MRS in mixed epilepsy populations, non-lesional epilepsy, influences of treatment on metabolite levels, altered consciousness, and practical aspects of the method.

Across multiple studies involving patients with different epilepsy syndromes, decreased tNAA or tNAA-containing metabolite ratios were the most common findings, reflecting generalized alterations of neuronal function in patients with epilepsy[8,206–213]. In particular, deviations in neuronal metabolism were frequently observed in patients with a normal MRI, although their distribution varied across epilepsy populations[207,211,212,214]. Overall, the majority of studies found only limited value in conventional metabolites for differential diagnosis of focal and generalized epilepsies, while their association with seizure burden, neuronal damage, or pharmacoresistance was more prominent[8,209–211,214–217]. Similarly, in pediatric populations, metabolic changes typical for mesial temporal lobe epilepsy were found across patients with and without complex febrile Holopainen status epilepticus, suggesting that the former condition was more closely linked to epilepsy in general rather than specific febrile seizures[207].

The effects of antiepileptic treatment were another major topic of investigation[208,215,218–223]. In particular, studies that evaluated the ketogenic diet demonstrated the feasibility of detecting cerebral ketone bodies using MRS, with brain β-hydroxybutyrate strongly correlating with serum levels[208,222]. In contrast, valproate treatment was associated with decreases in mI and, in one study, increased Gln, potentially reflecting alterations in ammonia metabolism and osmoregulation in astrocytes[220,221]. Multiple reports directly evaluated the impact of anti-epileptic treatment on metabolite levels, illustrating that these effects were often prominent and should be taken into account during interpretation[208,215,218–223].

In contrast to the investigations that targeted specific epilepsy syndromes, one study focused on alterations of metabolism in networks associated with impaired consciousness[209]. Across different seizure types involving impaired consciousness, decreased tNAA ratios were found in the thalami and the upper brainstem[209]. This finding was consistent across different types of seizures that involved loss of consciousness, with only minor differences observed between these groups[209]. Thus, these findings suggested the involvement of consciousness-related thalamo-brainstem networks in impaired consciousness[209].

Finally, several reports evaluated the value of MRS in clinical practice beyond the identification of specific epilepsy syndromes[8,211,212,214]. Studies in pediatric and non-lesional epilepsy demonstrated that MRS could provide clinically meaningful information beyond conventional MRI, contributing to diagnosis, management, and prognosis[211,214]. In pediatric patients with seizures, MRS findings helped guide investigations to underlying metabolic or genetic disorders, differentiate neoplasia from cortical dysplasia, and assess prognosis in hypoxic-ischemic injury, even when conventional MRI findings were normal or inconclusive[214]. In non-

lesional pediatric epilepsy, MRS showed limited diagnostic value but revealed associations between reduced NAA/Cr ratios in the basal ganglia and white matter and drug resistance, suggesting potential prognostic utility[211].

3.6 Other metabolic MRI modalities

Twenty-seven studies evaluated other metabolic MRI:[31]P-MRS (n=13), CEST imaging (n=7), [23]Na-MRI (n=3), [13]C-MRS (n=3). and DMI (n=1). Each of these methods has the potential to provide additional insights into the metabolic processes not captured by standard [1]H-MRS. The biological targets and clinical applications of individual metabolic imaging methods are summarized in Figure 13. Due to the great between-study variability in the acquisition protocols and outcome parameters, the results could not be synthesized in a quantitative manner and thus we conducted a narrative synthesis instead.

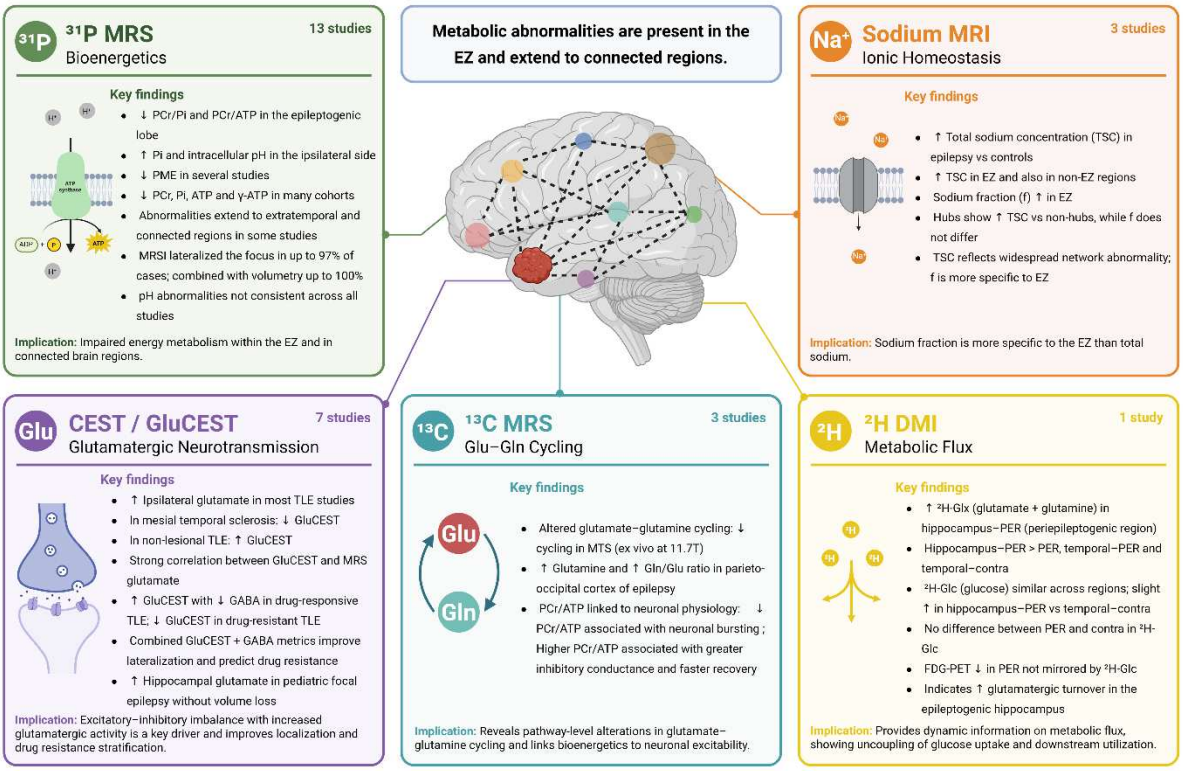


Figure 13. Overview of findings from non-proton metabolic MRI modalities in epilepsy. Abbreviations: [31]P MRS: phosphorus-31 magnetic resonance spectroscopy; [13]C MRS: carbon-13 magnetic resonance spectroscopy; [2]H DMI: deuterium metabolic imaging; MRI: magnetic resonance imaging; MRSI: magnetic resonance spectroscopic imaging; CEST: chemical exchange saturation transfer; GluCEST: glutamate chemical exchange saturation transfer; EZ: epileptogenic zone; PCr: phosphocreatine; Pi: inorganic phosphate; ATP: adenosine triphosphate; γ-ATP: gamma adenosine triphosphate; PME: phosphomonoesters; TSC: total sodium concentration; Glu: glutamate; Gln: glutamine; GABA: γ-aminobutyric acid; TLE: temporal lobe epilepsy; MTS: mesial temporal sclerosis; AUC: area under the curve; PER:

periepileptogenic region; Glx: glutamate plus glutamine; Glc: glucose; FDG-PET: fluorodeoxyglucose positron emission tomography. Created in BioRender. Rahnemayan, S. (2026) https://BioRender.com/nl83z8t

The available evidence demonstrated prominent metabolic abnormalities within the epileptogenic region, with abnormalities frequently extending into anatomically and functionally connected brain regions, supporting epilepsy as a network disorder rather than a purely focal disease[224–236]. ^{31}P-MRS identified widespread disturbances in cerebral energy metabolism, including altered PCr, ATP and inorganic phosphate[224–233,237,238]. Sodium MRI demonstrated increased total sodium concentration across epileptogenic and non-epileptogenic regions[234–236], whereas the short-T2 sodium signal fraction (f), a putative marker of sodium homeostasis, was selectively increased in the epileptogenic zone[235,236]. CEST/GluCEST imaging detected metabolically relevant CEST abnormalities with high spatial specificity, while GluCEST studies demonstrated focal glutamatergic alterations and promising performance for seizure-focus lateralization, including in MRI-negative epilepsy; one recent multimodal study also demonstrated potential for drug-resistance stratification[239–245].
Although investigated in relatively few studies, ^{13}C-MRS and deuterium metabolic imaging provided complementary mechanistic insights that are not accessible with conventional ^{1}H-MRS[246–249]. ^{13}C-MRS demonstrated abnormalities of glutamate–glutamine metabolism and cycling (Petroff, 2002; Otsuki, 2005), while complementary bioenergetic measurements linked reduced PCr/ATP to greater neuronal bursting and impaired inhibitory function[248]. Deuterium metabolic imaging revealed increased glutamatergic turnover in the hippocampus, despite relatively preserved glucose uptake, suggesting uncoupling between glucose delivery and downstream metabolism in epileptogenic tissue[249]. Together, these emerging techniques provide complementary information on neuronal metabolism and network dysfunction, although further validation in larger clinical cohorts is required[234–236,239–249].

4. Discussion

The present systematic review included 298 articles on metabolic MRI in epilepsy. The review demonstrated both the strengths and the current limitations of metabolic MRI while also highlighting the progress made in the field over the last three decades. Despite significant heterogeneity in the populations, approaches, and analyses, the review revealed a consensus about the nature of metabolic abnormalities in epilepsy. Early studies focused on identifying metabolic abnormalities within the epileptogenic region, while the later studies demonstrated that these abnormalities often occur in distributed networks[12,15,22,55,68,71,74,77]. In focal, generalized, MRI-negative, and tumor-related epilepsies, metabolic alterations identified in these networks highlight the concept of epilepsy as a connectopathy[15,22,68,74,77,185,186,199,200]. Metabolic MRI provides a unique link between structural, functional, and biochemical abnormalities in epilepsy.

Despite the general similarity of network dysfunction in different epilepsies, the review demonstrated that each category of epilepsies has its unique metabolic fingerprint. The reduction of NAA was a universal marker of neuronal dysfunction in all epilepsies, while other metabolites were changed differently in focal, generalized, and tumor-related epilepsies[9,12,15,67,74,176,178,183,199]. The focal epilepsies were characterized by the most diverse patterns of metabolite changes that reflect the combined dysfunction of glutamatergic, GABAergic, glycinergic, and cholinergic systems, as well as astroglial, membrane, and energy metabolism[16,49,67,69,77,80–82,84,250]. The pattern was most prominent in the epileptogenic core and gradually changed (became less prominent) with increasing distance from the lesion[9,15,68,69,81,251]. In contrast, generalized epilepsies were associated with relatively uniform decreases of NAA in the thalamo-cortical network with less prominent changes of other metabolites[172–187]. The pattern of tumor-related epilepsy was even more different, with recent studies reporting increased Glu-, Glx-, and Glx/GABA-related measures associated with epileptogenicity[197–200]. Thus, the review demonstrated that the alterations of neuronal metabolism are a common signature of epilepsies, while the changes of glutamatergic transmission, astroglial function, and energy metabolism are more specific to certain categories of epilepsies.

Different metabolites reflect different aspects of metabolic dysfunction. While the reduction of NAA was traditionally linked to neuronal loss, the post-surgery recovery of this marker and its presence in normal brain regions indicate that decreased NAA levels are often related to reversible neuronal and mitochondrial dysfunction[11,13,75,78,79]. In contrast, Glu, GABA, mI, Cho, Cr, lactate, and phosphorus-containing metabolites were more variable, reflecting the changes of excitatory and inhibitory neurotransmission, astroglial proliferation and membrane turnover, energy metabolism, and other processes[16,49,67,69,77,80–82,84,250]. The different aspects of

metabolic dysfunction were also reflected in the associations between metabolites and cognitive performance, treatment response, and seizure outcome. Specifically, the review demonstrated that levels of hippocampal NAA were consistently linked to memory performance, while the metabolites in the frontal, cingulate, and occipital cortex were associated with language, mood, processing speed, and overall cognition[111–125,127]. Thus, cognitive impairments in epilepsy are better understood as the dysfunction of distributed networks rather than isolated memory problems. Similarly, different treatments primarily affect different aspects of metabolic dysfunction. GABA-related metabolites were most frequently affected by pharmacological interventions, while the normalization of NAA levels was most prominent after surgery[11,13,14,128–131,134–137,139,140,142,147–149].

The review also demonstrated that the spatial pattern of metabolite changes better reflects the clinical outcome than the mere presence of metabolic abnormalities[133,140,151,152,154–158,160,161]. In particular, the studies of surgical outcome revealed that the patients with focal epilepsy who had localized (rather than distributed) metabolic abnormalities concordant with the epileptogenic zone and normalization of metabolites after surgery had a better outcome[13,14,133,151,156,157,159,160]. In contrast, the involvement of multiple brain regions and the persistence of metabolic abnormalities after surgery were associated with a poorer outcome[133,140,152,154–156,158,161]. Thus, the pattern of metabolite changes is indicative of the response to treatment.

Importantly, the review demonstrated that different methods of metabolic MRI provide complementary information about the nature of metabolic abnormalities. ^{1}H-MRS remains the workhorse of metabolic MRI in epilepsy research and clinical practice. The review demonstrated that ^{31}P-MRS provides valuable information about bioenergetics[224–233,237,238], while sodium MRI can help understand ionic dysregulation[234–236]. CEST imaging is more specific to glutamatergic abnormalities[239–245], while ^{13}C-MRS and deuterium metabolic imaging can provide *in vivo* information about Glu-Gln cycling, metabolic flux, and other aspects of metabolic dysfunction[246,247,249]. Thus, different techniques of metabolic MRI help characterize various aspects of the same problem and, therefore, should be used together to obtain a comprehensive understanding of metabolic abnormalities in epilepsy.

Our scientometric analysis demonstrated that the field of metabolic MRI in epilepsy has evolved considerably in the last three decades. The focus of research has shifted from small studies of a few patients using regional spectroscopy to large-scale studies that utilize ultra-high-field MRI, volumetric spectroscopy, multinuclear MRI, and more advanced quantitative approaches. At the same time, the questions addressed by these studies have become more diverse, ranging from the localization of epileptogenic regions to the analysis of cognitive performance and treatment outcome. Future studies of metabolic epilepsy will likely combine different approaches, including various metabolic imaging techniques, structural and

functional MRI, electrophysiology, and machine-learning, to characterize the endophenotype of epilepsy in greater detail.

The main limitation of this review is the heterogeneity of the included studies. Most of the analyzed articles differed substantially in terms of populations, epilepsy types, MRI approaches, field strengths, voxel placement, metabolite quantification, and analyses. This heterogeneity limited our ability to perform a formal meta-analysis. The methodological quality of the included studies was generally sufficient (according to the MMAT tool), but the variability in the reporting of the methods and results (according to the MRS-Q tool) hindered the comparison of the studies. In particular, the differences in the reporting of acquisition details, quality control procedures, partial-volume correction, and metabolite quantification made the comparison of certain aspects of the included studies difficult. Furthermore, most of the studies used the same populations (drug-resistant temporal lobe epilepsy), while other categories of epilepsies, such as generalized epilepsies, were understudied. The same limitation applied to pediatric epilepsy and tumor-related epilepsy. Therefore, despite the overall consistency in the conclusions about the distributed nature of metabolic abnormalities in epilepsy, future research should prioritize multicenter studies that use standardized acquisition, processing, and quantification methods, alongside transparent reporting, in accordance with established recommendations, such as the MRSinMRS guidelines[2,252] .

Drawing on the findings of this systematic review, we identify several research priorities that, in our view, warrant particular attention. First, multicentre validation should focus on well-characterized populations, particularly unilateral mesial temporal lobe epilepsy, where metabolic abnormalities have been most extensively investigated. Harmonized protocols and prospective follow-up could establish reproducibility and determine whether metabolic imaging improves epileptogenic zone localization and postoperative outcome prediction beyond conventional assessments. Subsequent studies should extend to more challenging populations, including MRI-negative focal epilepsy and focal cortical dysplasia.

Second, although reduced tNAA was among the most consistently reported findings, its predominance may partly reflect its relatively high signal-to-noise ratio and historical emphasis rather than superior biological specificity. Future studies should systematically assess whether Glu, Gln, GABA, and other metabolites provide complementary diagnostic or prognostic information.

Third, metabolic alterations should be investigated beyond the presumed epileptogenic core, including perilesional, ipsilateral, contralateral, and remote network regions. Whole-brain 7T MRSI offers opportunities for such investigations, while non-proton techniques may provide complementary insights into energy metabolism and ionic homeostasis.

Finally, methodological studies should establish application-specific requirements for spatial resolution, spectral quality, and metabolite quantification. Rather than maximizing spatial

resolution alone, future protocols should balance anatomical specificity against signal-to-noise ratio, measurement uncertainty, and acquisition time, particularly for challenging metabolites. Standardized quality-control criteria and test–retest assessments will be essential for reliable multicentre comparisons.

5. Conclusions

Metabolic MRI provides converging evidence for distributed neurochemical abnormalities across epilepsy syndromes despite considerable heterogeneity in imaging methods and study design. Reduced NAA is the most consistentlt reported marker of neuronal dysfunction, whereas alterations in glutamatergic neurotransmission, gliosis, membrane turnover, bioenergetics, and ionic homeostasis distinguished different epilepsy subtypes and reflected complementary aspects of epileptogenic biology. Rather than identifying a single metabolic biomarker, the available evidence supports a network-based metabolic framework in which different metabolic imaging techniques interrogate distinct but interconnected biological processes. Future progress will therefore depend not only on advances such as ultra-high-field MRI, whole-brain spectroscopic imaging, multinuclear MRI, and multimodal integration, but also on greater methodological harmonization to enable robust, reproducible, and clinically translatable metabolic biomarkers for epilepsy.

References

1. Hyder, F. & Rothman, D. L. Advances in imaging brain metabolism. *Annu. Rev. Biomed. Eng.* **19**, 485–515 (2017).
2. Talos, I. F. *et al.* Magnetic resonance and the human brain: anatomy, function and metabolism. *Cell. Mol. Life Sci.* **63**, 1106–1124 (2006).
3. Hugg, J. W., Laxer, K. D., Matson, G. B., Maudsley, A. A. & Weiner, M. W. Neuron loss localizes human temporal lobe epilepsy by in vivo proton magnetic resonance spectroscopic imaging. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society* **34**, 788–794 (1993).
4. Ng, T. C. *et al.* Temporal lobe epilepsy: presurgical localization with proton chemical shift imaging. *Radiology* **193**, 465–472 (1994).
5. Hetherington, H. *et al.* Proton nuclear magnetic resonance spectroscopic imaging of human temporal lobe epilepsy at 4.1 T. *Ann. Neurol.* **38**, 396–404 (1995).
6. Cendes, F., Stanley, J. A., Dubeau, F., Andermann, F. & Arnold, D. L. Proton magnetic resonance spectroscopic imaging for discrimination of absence and complex partial seizures. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society* **41**, 74–81 (1997).
7. Li, L. M. *et al.* Neuronal metabolic dysfunction in patients with cortical developmental malformations: a proton magnetic resonance spectroscopic imaging study. *Neurology* **50**, 755–759 (1998).
8. Stanley, J. A., Cendes, F., Dubeau, F., Andermann, F. & Arnold, D. L. Proton magnetic resonance spectroscopic imaging in patients with extratemporal epilepsy. *Epilepsia* **39**, 267–273 (1998).
9. Hugg, J. W. *et al.* Normalization of contralateral metabolic function following temporal lobectomy demonstrated by 1H magnetic resonance spectroscopic imaging. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society* **40**, 236–239 (1996).
10. Cendes, F., Caramanos, Z., Andermann, F., Dubeau, F. & Arnold, D. L. Proton magnetic resonance spectroscopic imaging and magnetic resonance imaging volumetry in the lateralization of temporal lobe epilepsy: a series of 100 patients. *Ann. Neurol.* **42**, 737–746 (1997).
11. Cendes, F., Andermann, F., Dubeau, F., Matthews, P. M. & Arnold, D. L. Normalization of neuronal metabolic dysfunction after surgery for temporal lobe epilepsy: evidence from proton MR spectroscopic imaging. *Neurology* **49**, 1525–1533 (1997).
12. Serles, W. *et al.* Time course of postoperative recovery of N-acetyl-aspartate in temporal lobe epilepsy. *Epilepsia* **42**, 190–197 (2001).

13. Huang, H. *et al.* Simultaneous high-resolution whole-brain MR spectroscopy and [18F]FDG PET for temporal lobe epilepsy. *Eur. J. Nucl. Med. Mol. Imaging* **51**, 721–733 (2024).
14. Chambers, S. *et al.* Glutamine Metabolism and Metabolic Profiling Using 7 T CRT-FID MRSI in Focal Epilepsy. *Eur. J. Neurol.* **32**, (2025).
15. Bartusik-Aebisher, D. *et al.* Multinuclear NMR and MRI Beyond Proton Imaging: Principles, Contrast Mechanisms, and Applications in Materials and Biomedicine. *Int. J. Mol. Sci.* **27**, 4384 (2026).
16. Veeraiah, P. & Jansen, J. F. A. Multinuclear magnetic resonance spectroscopy at ultra-high-field: assessing human cerebral metabolism in healthy and diseased states. *Metabolites* **13**, 577 (2023).
17. De Graaf, R. A. In vivo NMR spectroscopy. *Principles and techniques* **2**, (2007).
18. Desale, P. *et al.* Navigating neural landscapes: A comprehensive review of magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) applications in epilepsy. *Cureus* **16**, (2024).
19. Pan, J. W. *et al.* Neurometabolism in human epilepsy. *Epilepsia* **49**, 31–41 (2008).
20. Pan, J. W. *et al.* Metabolic networks in epilepsy by MR spectroscopic imaging. *Acta Neurol. Scand.* **126**, 411–420 (2012).
21. Engel Jr, J. *et al.* Connectomics and epilepsy. *Curr. Opin. Neurol.* **26**, 186 (2013).
22. Pan, J. W. & Kuzniecky, R. I. Utility of magnetic resonance spectroscopic imaging for human epilepsy. *Quant. Imaging Med. Surg.* **5**, 313 (2015).
23. Wang, K., Wei, P., Shan, Y. & Zhao, G. Epileptic networks neurosurgery: connectomes and hubs. Preprint at (2022).
24. Duncan, J. S., Winston, G. P., Koepp, M. J. & Ourselin, S. Brain imaging in the assessment for epilepsy surgery. *Lancet Neurol.* **15**, 420–433 (2016).
25. Page, M. J. *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *bmj* **372**, (2021).
26. Schiavo, J. H. PROSPERO: an international register of systematic review protocols. *Med. Ref. Serv. Q.* **38**, 171–180 (2019).
27. Ouzzani, M., Hammady, H., Fedorowicz, Z. & Elmagarmid, A. Rayyan—a web and mobile app for systematic reviews. *Syst. Rev.* **5**, 210 (2016).
28. Hong, Q. N. *et al.* The Mixed Methods Appraisal Tool (MMAT) version 2018 for information professionals and researchers. *Education for information* **34**, 285–291 (2018).
29. Peek, A. L. *et al.* Brain GABA and glutamate levels across pain conditions: A systematic literature review and meta-analysis of 1H-MRS studies using the MRS-Q quality assessment tool. *Neuroimage* **210**, 116532 (2020).
30. Führer, C., Fuhrer, C., Solem, J. E. & Verdier, O. *Scientific Computing with Python: High-Performance Scientific Computing with NumPy, SciPy, and Pandas*. (Packt Publishing Ltd, 2021).

31. Vielhaber, S. *et al.* Subfield-specific Loss of Hippocampal N-acetyl Aspartate in Temporal Lobe Epilepsy. *academia.edu* **49**, 40–50 (2008).
32. Vainio, P. *et al.* Reduced/V-acetylaspartate concentration in temporal lobe epilepsy by quantitative 1H MRS in vivo. *Neuroreport* **5**, 1733–1736 (1994).
33. Gadian, D. G. *et al.* H magnetic resonance spectroscopy in the investigation of intractable epilepsy. *Acta Neurol. Scand.* **89**, 116–121 (1994).
34. Duc, C. O. *et al.* Quantitative 1H MRS in the evaluation of mesial temporal lobe epilepsy in vivo. *Magn. Reson. Imaging* **16**, 969–979 (1998).
35. Chang, K.-H. *et al.* Usefulness of single voxel proton MR spectroscopy in the evaluation of hippocampal sclerosis. *Korean J. Radiol.* **1**, 25–32 (2000).
36. Hammen, T. *et al.* Non-invasive detection of hippocampal sclerosis: correlation between metabolite alterations detected by 1H-MRS and neuropathology. *Wiley Online LibraryT Hammen, M Hildebrandt, A Stadlbauer, M Doelken, T Engelhorn, F Kerling, B KasperNMR in Biomedicine: An International Journal Devoted to the …, 2008•Wiley Online Library* **21**, 545–552 (2008).
37. Connelly, A. *et al.* Proton magnetic resonance spectroscopy in MRI-negative temporal lobe epilepsy. *Neurology* **51**, 61–66 (1998).
38. Woermann, F. G. *et al.* Short echo time single-voxel 1H magnetic resonance spectroscopy in magnetic resonance imaging–negative temporal lobe epilepsy: Different biochemical profile compared with hippocampal sclerosis. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society* **45**, 369–376 (1999).
39. Savic, I. *et al.* In vivo measurements of glutamine+ glutamate (Glx) and N-acetyl aspartate (NAA) levels in human partial epilepsy. *Acta Neurol. Scand.* **102**, 179–188 (2000).
40. Shih, J. J. *et al.* Areas of interictal spiking are associated with metabolic dysfunction in MRI-negative temporal lobe epilepsy. *Epilepsia* **45**, 223–229 (2004).
41. Hammen, T. *et al.* Identifying the affected hemisphere by 1H-MR spectroscopy in patients with temporal lobe epilepsy and no pathological findings in high resolution MRI. *Eur. J. Neurol.* **13**, 482–490 (2006).
42. Simister, R. J., McLean, M. A., Barker, G. J. & Duncan, J. S. Proton magnetic resonance spectroscopy of malformations of cortical development causing epilepsy. *Epilepsy Res.* **74**, 107–115 (2007).
43. Colon, A. J. *et al.* MRS-lateralisation index in patients with epilepsy and focal cortical dysplasia or a MEG-focus using bilateral single voxels. *Epilepsy Res.* **89**, 148–153 (2010).
44. Tschampa, H. J. *et al.* Proton magnetic resonance spectroscopy in focal cortical dysplasia at 3 T. *Seizure* **32**, 23–29 (2015).

45. Aun, A. A. K. *et al.* Role of magnetic resonance spectroscopy (MRS) in nonlesional temporal lobe epilepsy. *The Egyptian Journal of Radiology and Nuclear Medicine* **47**, 217–231 (2016).
46. Tan, Q. *et al.* Quantitative 1H-MRS reveals metabolic difference between subcategories of malformations of cortical development. *Neuroradiology* **63**, 1539–1548 (2021).
47. Wu, S. *et al.* γ-Aminobutyric acid as a biomarker of the lateralizing and monitoring drug effect in patients with magnetic resonance imaging-negative temporal lobe epilepsy. *Front. Neurosci.* **17**, 1184440 (2023).
48. Pu, H. *et al.* Metabolic heterogeneity in different subtypes of malformations of cortical development causing epilepsy: a proton magnetic resonance spectroscopy study. *Quant. Imaging Med. Surg.* **13**, 8625–8640 (2023).
49. Reda, A. M., Elsharkawy, A. & Hasby, S. E. Usefulness of combined diffusion tensor imaging, arterial spin labelling and spectroscopic interictal analysis in refractory epilepsy. *Egyptian Journal of Radiology and Nuclear Medicine 2023 54:1* **54**, 45- (2023).
50. Connelly, A., Jackson, G. D., Duncan, J. S., King, M. D. & Gadian, D. G. Magnetic resonance spectroscopy in temporal lobe epilepsy. *Neurology* **44**, 1411–1417 (1994).
51. Lu, D. *et al.* Temporal lobe epilepsy: correlation of proton magnetic resonance spectroscopy and 18F-fluorodeoxyglucose positron emission tomography. *Magn. Reson. Med.* **37**, 18–23 (1997).
52. Someya, Y. *et al.* Seizure frequency and bilateral temporal abnormalities: a proton magnetic resonance spectroscopy of temporal lobe epilepsy. *Seizure* **9**, 274–279 (2000).
53. Capizzano, A. A. *et al.* Multisection proton MR spectroscopy for mesial temporal lobe epilepsy. *American journal of neuroradiology* **23**, 1359–1368 (2002).
54. Abo El-Kasem, R., Maghrabi, M. G., Elmalah, H. E. G., Badry, R. & Farghaly, S. Quantitative MRI assessment of idiopathic temporal lobe epilepsy: comparative study between automated MR volumetry and proton MR spectroscopy over conventional measures. *Egyptian Journal of Radiology and Nuclear Medicine 2025 56:1* **56**, 59- (2025).
55. Bartnik-Olson, B. L., Ding, D., Howe, J., Shah, A. & Losey, T. Glutamate metabolism in temporal lobe epilepsy as revealed by dynamic proton MRS following the infusion of [U13-C] glucose. *Epilepsy Res.* **136**, 46–53 (2017).
56. Dölken, M. *et al.* 1H-MRS profile in MRI positive versus MRI negative patients with temporal lobe epilepsy. *RöFo - Fortschritte auf dem Gebiet der Röntgenstrahlen und der bildgebenden Verfahren* **180**, VO_407_6 (2008).
57. Xu, M. Y. *et al.* Proton MR Spectroscopy in Patients with Structural MRI-Negative Temporal Lobe Epilepsy. *J. Neuroimaging* **25**, 1030–1037 (2015).

58. Holopainen, I. E. *et al.* Temporal lobe pathology in epilepsy: proton magnetic resonance spectroscopy and positron emission tomography study. *Pediatr. Neurol.* **16**, 98–104 (1997).
59. Achten, E. *et al.* Single-voxel proton MR spectroscopy and positron emission tomography for lateralization of refractory temporal lobe epilepsy. *American journal of neuroradiology* **19**, 1–8 (1998).
60. Bakken, I. J. *et al.* Applications of neural network analyses to in vivo 1H magnetic resonance spectroscopy of epilepsy patients. *Epilepsy Res.* **35**, 245–252 (1999).
61. Xin, L. *et al.* Neurochemical characteristics of pathological tissues in epilepsy: A preliminary 1H MR spectroscopy study at 7 T. *Eur. J. Radiol. Open* **14**, 100640 (2025).
62. Pradhan, N. *et al.* Investigation of in-vivo GABA+ and Glutamate levels in patients with drug resistant unilateral temporal lobe epilepsy using MEGA-PRESS and correlates with clinical semiology. *Epilepsy Res.* **218**, (2025).
63. Castillo, M., Smith, J. K. & Kwock, L. Proton MR spectroscopy in patients with acute temporal lobe seizures. *American journal of neuroradiology* **22**, 152–157 (2001).
64. Cendes, F., Andermann, F., Preul, M. C. & Arnold, D. L. Lateralization of temporal lobe epilepsy based on regional metabolic abnormalities in proton magnetic resonance spectroscopic images. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society* **35**, 211–216 (1994).
65. Woermann, F. G., McLean, M. A., Bartlett, P. A., Barker, G. J. & Duncan, J. S. Quantitative short echo time proton magnetic resonance spectroscopic imaging study of malformations of cortical development causing epilepsy. *Brain* **124**, 427–436 (2001).
66. Guye, M. *et al.* Metabolic and electrophysiological alterations in subtypes of temporal lobe epilepsy: a combined proton magnetic resonance spectroscopic imaging and depth electrodes study. *Epilepsia* **43**, 1197–1209 (2002).
67. Mueller, S. G. *et al.* Metabolic characteristics of cortical malformations causing epilepsy. *J. Neurol.* **252**, 1082–1092 (2005).
68. Krsek, P. *et al.* 1H MR Spectroscopic Imaging in Patients with MRI-Negative Extratemporal Focal Epilepsy. *researchgate.net* **17**, 2126–2135 (2007).
69. Li, L. M., Cendes, F., Andermann, F., Dubeau, F. & Arnold, D. L. Spatial extent of neuronal metabolic dysfunction measured by proton MR spectroscopic imaging in patients with localization-related epilepsy. *Epilepsia* **41**, 666–674 (2000).
70. Mueller, S. G. *et al.* Identification of abnormal neuronal metabolism outside the seizure focus in temporal lobe epilepsy. *Epilepsia* **45**, 355–366 (2004).
71. Guye, M. *et al.* 1H-MRS imaging in intractable frontal lobe epilepsies characterized by depth electrode recording. *Neuroimage* **26**, 1174–1183 (2005).

72. Hetherington, H. P. *et al.* A subcortical network of dysfunction in TLE measured by magnetic resonance spectroscopy. *neurology.orgHP Hetherington, RI Kuzniecky, K Vives, O Devinsky, S Pacia, D Luciano, B VasquezNeurology, 2007•neurology.org* **69**, 2256–2265 (2007).

73. Maudsley, A. A., Domenig, C., Ramsay, R. E. & Bowen, B. C. Application of volumetric MR spectroscopic imaging for localization of neocortical epilepsy. *Epilepsy Res.* **88**, 127–138 (2010).

74. Mueller, S. G. *et al.* Widespread extrahippocampal NAA/(Cr+Cho) abnormalities in TLE with and without mesial temporal sclerosis. *J. Neurol.* **258**, 603 (2010).

75. Mohamed, R. E. el dein, Aboelsafa, A. A. & Dawoud, R. M. Arterial spin-labelling and magnetic resonance spectroscopy as imaging biomarkers for detection of epileptogenic zone in non-lesional focal impaired awareness epilepsy. *Egyptian Journal of Radiology and Nuclear Medicine 2020 51:1* **51**, 200- (2020).

76. Kuzniecky, R. *et al.* Magnetic resonance spectroscopic imaging in temporal lobe epilepsy: neuronal dysfunction or cell loss? *Arch. Neurol.* **58**, 2048–2053 (2001).

77. Cohen-Gadol, A. A., Pan, J. W., Kim, J. H., Spencer, D. D. & Hetherington, H. H. Mesial temporal lobe epilepsy: a proton magnetic resonance spectroscopy study and a histopathological analysis. *J. Neurosurg.* **101**, 613–620 (2004).

78. Simister, R. J. *et al.* A short-echo-time proton magnetic resonance spectroscopic imaging study of temporal lobe epilepsy. *Epilepsia* **43**, 1021–1031 (2002).

79. Shen, J. *et al.* Use of Short Echo Time Two-Dimensional 1H-Magnetic Resonance Spectroscopy in Temporal Lobe Epilepsy with Negative Magnetic Resonance Imaging Findings. *journals.sagepub.comJ Shen, L Zhang, X Tian, J Liu, X Ge, X ZhangJournal of International Medical Research, 2009•journals.sagepub.com* **37**, 1211–1219 (2009).

80. Aydin, H. *et al.* Value of Proton-MR-Spectroscopy in the Diagnosis of Temporal Lobe Epilepsy; Correlation of Metabolite Alterations With Electroencephalography. *Iranian Journal of Radiology* **9**, 1 (2012).

81. Jansen, J. F. A. *et al.* Quantitative MR and cognitive impairment in cryptogenic localisation-related epilepsy. *Epileptic Disord.* **16**, 318–327 (2014).

82. van Veenendaal, T. M. *et al.* High field imaging of large-scale neurotransmitter networks: Proof of concept and initial application to epilepsy. *Neuroimage Clin.* **19**, 47–55 (2018).

83. Sharma, A. A., Nenert, R., Goodman, A. & Szaflarski, J. P. Concordance between focal brain temperature elevations and focal edema in temporal lobe epilepsy. *Epilepsia* **64**, 1289–1304 (2023).

84. Mueller, C. *et al.* Brain temperature, brain metabolites, and immune system phenotypes in temporal lobe epilepsy. *Epilepsia Open* **9**, 2454–2466 (2024).

85. Cendes, F., Andermann, F., Dubeau, F. & Arnold, D. L. Proton magnetic resonance spectroscopic images and MRI volumetric studies for lateralization of temporal lobe epilepsy. *Magn. Reson. Imaging* **13**, 1187–1191 (1995).
86. Constantinidis, I. *et al.* Evaluation of 1H magnetic resonance spectroscopic imaging as a diagnostic tool for the lateralization of epileptogenic seizure foci. *Br. J. Radiol.* **69**, 15–24 (1996).
87. Chu, W. *et al.* Statistically driven identification of focal metabolic abnormalities in temporal lobe epilepsy with corrections for tissue heterogeneity using 1H spectroscopic imaging. *Magnetic Resonance in Medicine: An Official Journal of the International Society for Magnetic Resonance in Medicine* **43**, 359–367 (2000).
88. Capizzano, A. A. *et al.* Temporal lobe epilepsy: qualitative reading of 1H MR spectroscopic images for presurgical evaluation. *Radiology* **218**, 144–151 (2001).
89. Mueller, S. G. *et al.* Identification of the epileptogenic lobe in neocortical epilepsy with proton MR spectroscopic imaging. *Epilepsia* **45**, 1580–1589 (2004).
90. Pereira, P. M. G., Oliveira, E. & Rosado, P. Relative localizing value of amygdalo-hippocampal MR biometry in temporal lobe epilepsy. *Epilepsy Res.* **69**, 147–164 (2006).
91. Leite, R. A. A., Otaduy, M. C. G., e Silva, G. E. G., Ferreira, M. L. B. & Aragão, M. de F. V. Proton magnetic spectroscopy agreed better with magnetic resonance image to lateralization of epileptogenic zone than with surface electroencephalography. *Arq. Neuropsiquiatr.* **71**, 584–590 (2013).
92. Eryurt, B. *et al.* Presurgical evaluation of mesial temporal lobe epilepsy with multiple advanced MR techniques at 3T. *Journal of Neuroradiology* **42**, 283–290 (2015).
93. Jamalipour Soufi, G., Hekmat Nia, A., Hajalikhani, P., Mehvari-Habibabadi, J. & Chit Saz, N. Correlation of magnetic resonance spectroscopy and magnetic resonance imaging with findings of electroencephalography in patients with temporal lobe epilepsy. *J. Med. Radiat. Sci.* **71**, 51 (2023).
94. Maton, B. *et al.* Correlation of scalp EEG and 1H-MRS metabolic abnormalities in temporal lobe epilepsy. *Epilepsia* **42**, 417–422 (2001).
95. Maton, B. *et al.* Postictal stability of proton magnetic resonance spectroscopy imaging (1H-MRSI) ratios in temporal lobe epilepsy. *Neurology* **56**, 251–253 (2001).
96. Vermathen, P., Laxer, K. D., Schuff, N., Matson, G. B. & Weiner, M. W. Evidence of neuronal injury outside the medial temporal lobe in temporal lobe epilepsy: N-acetylaspartate concentration reductions detected with multisection proton MR spectroscopic imaging—initial experience. *Radiology* **226**, 195–202 (2003).
97. Mueller, S. G. *et al.* Spectroscopic metabolic abnormalities in mTLE with and without MRI evidence for mesial temporal sclerosis using hippocampal short-TE MRSI. *Epilepsia* **44**, 977–980 (2003).

98. Leite, C. D. C., Lucato, L. T., Sato, J. R., Valente, K. D. & Otaduy, M. C. G. Multivoxel proton MR spectroscopy in malformations of cortical development. *AJNR Am. J. Neuroradiol.* **28**, 1071–1075 (2007).

99. Hsu, Y.-Y. *et al.* Proton MR spectroscopy in patients with complex partial seizures: single-voxel spectroscopy versus chemical-shift imaging. *American journal of neuroradiology* **20**, 643–651 (1999).

100. Petroff, O. A. C., Spencer, D. D., Alger, J. R. & Prichard, J. W. High-field proton magnetic resonance spectroscopy of human cerebrum obtained during surgery for epilepsy. *Neurology* **39**, 1197–1202 (1989).

101. Peeling, J. & Sutherland, G. High-resolution 1H NMR spectroscopy studies of extracts of human cerebral neoplasms. *Magn. Reson. Med.* **24**, 123–136 (1992).

102. Petroff, O. A. C., Pleban, L. A. & Spencer, D. D. Symbiosis between in vivo and in vitro NMR spectroscopy: the creatine, N-acetylaspartate, glutamate, and GABA content of the epileptic human brain. *Magn. Reson. Imaging* **13**, 1197–1211 (1995).

103. Aasly, J. *et al.* Proton magnetic resonance spectroscopy of brain biopsies from patients with intractable epilepsy. *Epilepsy Res.* **35**, 211–217 (1999).

104. Petroff, O. A. C., Errante, L. D., Rothman, D. L., Kim, J. H. & Spencer, D. D. Neuronal and glial metabolite content of the epileptogenic human hippocampus. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society* **52**, 635–642 (2002).

105. Petroff, O. A. C., Errante, L. D., Kim, J. H. & Spencer, D. D. N-acetyl-aspartate, total creatine, and myo-inositol in the epileptogenic human hippocampus. *Neurology* **60**, 1646–1651 (2003).

106. Vielhaber, S. *et al.* Subfield-specific Loss of Hippocampal N-acetyl Aspartate in Temporal Lobe Epilepsy. *academia.edu* **49**, 40–50 (2008).

107. Wu, H. C. *et al.* Altered metabolomic-genomic signature: A potential noninvasive biomarker of epilepsy. *Epilepsia* **58**, 1626–1636 (2017).

108. Kirov, I. I. *et al.* Whole brain neuronal abnormalities in focal quantified with proton MR spectroscopy. *Epilepsy Res.* **139**, 85–91 (2018).

109. Gadian, D. G. *et al.* Lateralization of brain function in childhood revealed by magnetic resonance spectroscopy. *Neurology* **46**, 974–977 (1996).

110. Namer, I. J. *et al.* Combined measurements of hippocampal N-acetyl-aspartate and T2 relaxation time in the evaluation of mesial temporal lobe epilepsy: correlation with clinical severity and memory performances. *Epilepsia* **40**, 1424–1432 (1999).

111. Martin, R. C. *et al.* Cognitive correlates of 1H MRSI–detected hippocampal abnormalities in temporal lobe epilepsy. *Neurology* **53**, 2052 (1999).

112. Ferrier, C. H. *et al.* N-Acetylaspartate and creatine levels measured by 1H MRS relate to recognition memory. *Neurology* **55**, 1874–1883 (2000).
113. Pauli, E. *et al.* Chemical shift imaging spectroscopy and memory function in temporal lobe epilepsy. *Epilepsia* **41**, 282–289 (2000).
114. Sawrie, S. M. *et al.* Nonlinear trends in hippocampal metabolic function and verbal memory: evidence of cognitive reserve in temporal lobe epilepsy? *Epilepsy & Behavior* **1**, 106–111 (2000).
115. Sawrie, S. M. *et al.* Visual confrontation naming and hippocampal function: a neural network study using quantitative 1H magnetic resonance spectroscopy. *Brain* **123**, 770–780 (2000).
116. Kikuchi, S., Kubota, F., Hattori, S., Oya, N. & Mikuni, M. A study of the relationship between metabolism using1H-MRS and function using several neuropsychological tests in temporal lobe epilepsy. *Seizure* **10**, 188–193 (2001).
117. Sawrie, S. M. *et al.* Relationships among hippocampal volumetry, proton magnetic resonance spectroscopy, and verbal memory in temporal lobe epilepsy. *Epilepsia* **42**, 1403–1407 (2001).
118. Hanoğlu, L. *et al.* Correlation between 1H MRS and memory before and after surgery in mesial temporal lobe epilepsy with hippocampal sclerosis. *Epilepsia* **45**, 632–640 (2004).
119. Mantoan, M. A. S. *et al.* Correlation between memory, proton magnetic resonance spectroscopy, and interictal epileptiform discharges in temporal lobe epilepsy related to mesial temporal sclerosis. *Epilepsy & Behavior* **16**, 447–453 (2009).
120. Taraschenko, O. *et al.* Hippocampal dysmetabolism contributes to cognitive loss in autoimmune encephalitis and focal temporal epilepsy. *Front. Neurol.* **16**, 1597928 (2025).
121. O'Neill, J. *et al.* 1H MRSI and social communication deficits in pediatric complex partial seizures. *Epilepsia* **52**, 1705–1714 (2011).
122. van Veenendaal, T. M. *et al.* Glutamate concentrations vary with antiepileptic drug use and mental slowing. *Epilepsy and Behavior* **64**, 200–205 (2016).
123. He, C. *et al.* Gamma-aminobutyric acid (GABA) changes in the hippocampus and anterior cingulate cortex in temporal lobe epilepsy patients. *Epilepsy and Behavior* **115**, (2021).
124. Gilliam, F. G. *et al.* Hippocampal 1H-MRSI correlates with severity of depression symptoms in temporal lobe epilepsy. *neurology.orgFG Gilliam, BM Maton, RC Martin, SM Sawrie, RE Faught, JW Hugg, M ViikinsaloNeurology, 2007•neurology.org* **68**, 364–368 (2007).
125. Oates, M., Sharma, A. A., Nenert, R., Mueller, C. & Szaflarski, J. P. An exploratory study of brain temperature and choline abnormalities in temporal lobe epilepsy patients with depressive symptoms. *Epilepsia Open* **8**, 1541–1555 (2023).
126. Petroff, O. A. C., Rothman, D. L., Behar, K. L., Collins, T. L. & Mattson, R. H. Human brain GABA levels rise rapidly after initiation of vigabatrin therapy. *Neurology* **47**, 1567–1571 (1996).

127. Petroff, O. A. C., Rothman, D. L., Behar, K. L., Lamoureux, D. & Mattson, R. H. The effect of gabapentin on brain gamma-aminobutyric acid in patients with epilepsy. *Ann. Neurol.* **39**, 95–99 (1996).
128. Petroff, O. A. C., Mattson, R. H., Behar, K. L., Hyder, F. & Rothman, D. L. Vigabatrin increases human brain homocarnosine and improves seizure control. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society* **44**, 948–952 (1998).
129. Petroff, O. A. C., Hyder, F., Mattson, R. H. & Rothman, D. L. Topiramate increases brain GABA, homocarnosine, and pyrrolidinone in patients with epilepsy. *Neurology* **52**, 473 (1999).
130. Verhoeff, N. P. L. G. *et al.* Effects of vigabatrin on the GABAergic system as determined by [123I] iomazenil SPECT and GABA MRS. *Epilepsia* **40**, 1433–1438 (1999).
131. Li, L. M., Dubeau, F., Andermann, F. & Arnold, D. L. Proton magnetic resonance spectroscopic imaging studies in patients with newly diagnosed partial epilepsy. *Epilepsia* **41**, 825–831 (2000).
132. Petroff, O. A. C., Hyder, F., Rothman, D. L. & Mattson, R. H. Effects of gabapentin on brain GABA, homocarnosine, and pyrrolidinone in epilepsy patients. *Epilepsia* **41**, 675–680 (2000).
133. Mueller, S. G. *et al.* Effects of vigabatrin on brain GABA+/CR signals in patients with epilepsy monitored by 1H-NMR-spectroscopy: responder characteristics. *Epilepsia* **42**, 29–40 (2001).
134. Petroff, O. A. C., Hyder, F., Rothman, D. L. & Mattson, R. H. Topiramate rapidly raises brain GABA in epilepsy patients. *Epilepsia* **42**, 543–548 (2001).
135. Vermathen, P. 1 *et al.* Temporal lobectomy for epilepsy: recovery of the contralateral hippocampus measured by 1H MRS. *Neurology* **59**, 633–636 (2002).
136. Hájek, M., Dezortová, M., Liščák, R., Vymazal, J. & Vladyka, V. 1H MR spectroscopy of mesial temporal lobe epilepsies treated with Gamma knife. *Eur. Radiol.* **13**, 994–1000 (2003).
137. Mueller, S. G. *et al.* Effects of vigabatrin on brain GABA+/Cr signals in focus-distant and focus-near brain regions monitored by 1H-NMR spectroscopy. *Eur. J. Neurol.* **10**, 45–52 (2003).
138. Spencer, D. C. *et al.* Temporal lobe magnetic resonance spectroscopic imaging following selective amygdalohippocampectomy for treatment-resistant epilepsy. *Acta Neurol. Scand.* **112**, 6–12 (2005).
139. Hoggard, N. *et al.* The clinical course after stereotactic radiosurgical amygdalohippocampectomy with neuroradiological correlates. *Neurosurgery* **62**, 336–344 (2008).
140. Simister, R. J., McLean, M. A., Barker, G. J. & Duncan, J. S. Proton MR spectroscopy of metabolite concentrations in temporal lobe epilepsy and effect of temporal lobe resection. *Epilepsy Res.* **83**, 168–176 (2009).
141. Doelken, M. T. *et al.* Alterations of intracerebral γ-aminobutyric acid (GABA) levels by titration with levetiracetam in patients with focal epilepsies. *Wiley Online LibraryMT Doelken, T Hammen, W Bogner, A Mennecke, A Stadlbauer, U Boettcher, A DoerflerEpilepsia, 2010•Wiley Online Library* **51**, 1477–1482 (2010).

142. Abuhaiba, S. I. *et al.* The impact of cathodal tDCS on the GABAergic system in the epileptogenic zone: A multimodal imaging study. *Front. Neurol.* **13**, (2022).
143. Hazany, S. *et al.* Brain Glutathione Increase and Seizure Burden Decrease in Patients with Intractable Epilepsy on Ketogenic Diet. *J. Epilepsy Res.* **13**, 1 (2023).
144. Sharma, A. A. & Szaflarski, J. P. The longitudinal effects of cannabidiol on brain temperature in patients with treatment-resistant epilepsy. *Epilepsy and Behavior* **151**, (2024).
145. Rothman, D. L., Petroff, O. A., Behar, K. L. & Mattson, R. H. Localized 1H NMR measurements of gamma-aminobutyric acid in human brain in vivo. *Proceedings of the national academy of sciences* **90**, 5662–5666 (1993).
146. Hyder, F., Petroff, O. A. C., Mattson, R. H. & Rothman, D. L. Localized 1H NMR measurements of 2-pyrrolidinone in human brain in vivo. *Magnetic Resonance in Medicine: an Official Journal of the International Society for Magnetic Resonance in Medicine* **41**, 889–896 (1999).
147. Petroff, O. A. C., Hyder, F., Collins, T., Mattson, R. H. & Rothman, D. L. Acute effects of vigabatrin on brain GABA and homocarnosine in patients with complex partial seizures. *Epilepsia* **40**, 958–964 (1999).
148. Petroff, O. A. C., Rothman, D. L., Behar, K. L., Hyder, F. & Mattson, R. H. Effects of valproate and other antiepileptic drugs on brain glutamate, glutamine, and GABA in patients with refractory complex partial seizures. *Seizure* **8**, 120–127 (1999).
149. Ende, G. R. *et al.* Temporal lobe epilepsy: bilateral hippocampal metabolite changes revealed at proton MR spectroscopic imaging. *Radiology* **202**, 809–817 (1997).
150. Kuzniecky, R. *et al.* Predictive value of 1H MRSI for outcome in temporal lobectomy. *Neurology* **53**, 694 (1999).
151. Li, L. M. *et al.* Prognostic value of proton magnetic resonance spectroscopic imaging for surgical outcome in patients with intractable temporal lobe epilepsy and bilateral hippocampal atrophy. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society* **47**, 195–200 (2000).
152. Eberhardt, K. E. *et al.* The significance of bilateral CSI changes for the postoperative outcome in temporal lobe epilepsy. *J. Comput. Assist. Tomogr.* **24**, 919–926 (2000).
153. Stefan, H. *et al.* Magnetic resonance spectroscopy and histopathological findings in temporal lobe epilepsy. *Epilepsia* **42**, 41–46 (2001).
154. Antel, S. B. *et al.* Predicting surgical outcome in temporal lobe epilepsy patients using MRI and MRSI. *Neurology* **58**, 1505–1512 (2002).
155. Kantarci, K. *et al.* Comparative diagnostic utility of 1H MRS and DWI in evaluation of temporal lobe epilepsy. *Neurology* **58**, 1745–1753 (2002).

156. Lee, S. K. *et al.* Effect of seizure on hippocampus in mesial temporal lobe epilepsy and neocortical epilepsy: an MRS study. *Neuroradiology* **47**, 916–923 (2005).

157. Lantz, G., Seeck, M. & Lazeyras, F. Extent of preoperative abnormalities and focus lateralization predict postoperative normalization of contralateral 1H-magnetic resonance spectroscopy metabolite levels in patients with temporal lobe epilepsy. *American journal of neuroradiology* **27**, 1766–1769 (2006).

158. Pan, J. W. *et al.* 7T MR spectroscopic imaging in the localization of surgical epilepsy. *Epilepsia* **54**, 1668–1678 (2013).

159. Pan, J. W. *et al.* MR spectroscopic imaging at 3 T and outcomes in surgical epilepsy. *NMR Biomed.* **34**, (2021).

160. Briellmann, R. S. *et al.* Hippocampal sclerosis: MR prediction of seizure intractability. *Wiley Online LibraryRS Briellmann, R Mark Wellard, RAJ Masterton, DF Abbott, SF Berkovic, GD JacksonEpilepsia, 2007•Wiley Online Library* **48**, 315–323 (2007).

161. Campos, B. A. G. *et al.* Proton MRS may predict AED response in patients with TLE. *Epilepsia* **51**, 783–788 (2010).

162. Pimentel-Silva, L. R. *et al.* Interactions between in vivo neuronal-glial markers, side of hippocampal sclerosis, and pharmacoresponse in temporal lobe epilepsy. *Epilepsia* **61**, 1008–1018 (2020).

163. Zhang, H. *et al.* Proton magnetic resonance spectroscopy for the prediction to drug responsiveness of mesial temporal lobe epilepsy according to ILAE definition. *Seizure* **138**, 120–126 (2026).

164. Petroff, O. A. C., Rothman, D. L., Behar, K. L. & Mattson, R. H. Low brain GABA level is associated with poor seizure control. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society* **40**, 908–911 (1996).

165. Garcia, P. A. *et al.* Correlation of seizure frequency with N-acetyl-aspartate levels determined by 1H magnetic resonance spectroscopic imaging. *Magn. Reson. Imaging* **15**, 475–478 (1997).

166. Mendes-Ribeiro, J. A., Soares, R., Simoes-Ribeiro, F. & Guimarães, M. L. Reduction in temporal N-acetylaspartate and creatine (or choline) ratio in temporal lobe epilepsy: does this 1H-magnetic resonance spectroscopy finding mean poor seizure control? *J. Neurol. Neurosurg. Psychiatry* **65**, 518–522 (1998).

167. Tasch, E. *et al.* Neuroimaging evidence of progressive neuronal loss and dysfunction in temporal lobe epilepsy. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society* **45**, 568–576 (1999).

168. Hammen, T. *et al.* 1H-MR Spectroscopy Indicates Severity Markers in Temporal Lobe Epilepsy: Correlations between Metabolic Alterations, Seizures, and Epileptic Discharges in EEG. *Wiley Online LibraryT Hammen, M Schwarz, M Doelken, F Kerling, T Engelhorn, A Stadlbauer, O GanslandtEpilepsia, 2007•Wiley Online Library* **48**, 263–269 (2007).

169. Schmidt, M. H., Crocker, C. E., Abdolell, M., Ghuman, M. S. & Pohlmann-Eden, B. Toward individualized prediction of seizure recurrence: Hippocampal neuroimaging features in a cohort of patients from a first seizure clinic. *Epilepsy and Behavior* **122**, (2021).

170. Savic, I., Lekvall, A., Greitz, D. & Helms, G. MR spectroscopy shows reduced frontal lobe concentrations of N-acetyl aspartate in patients with juvenile myoclonic epilepsy. *Epilepsia* **41**, 290–296 (2000).

171. Mory, S. B., Li, L. M., Guerreiro, C. A. M. & Cendes, F. Thalamic dysfunction in juvenile myoclonic epilepsy: a proton MRS study. *Epilepsia* **44**, 1402–1405 (2003).

172. Bernasconi, A. *et al.* Magnetic resonance spectroscopy and imaging of the thalamus in idiopathic generalized epilepsy. *Brain* **126**, 2447–2454 (2003).

173. Simister, R. J., McLean, M. A., Barker, G. J. & Duncan, J. S. Proton MRS reveals frontal lobe metabolite abnormalities in idiopathic generalized epilepsy. *Neurology* **61**, 897–902 (2003).

174. Savic, I., Österman, Y. & Helms, G. MRS shows syndrome differentiated metabolite changes in human-generalized epilepsies. *Neuroimage* **21**, 163–172 (2004).

175. Fojtiková, D., Brázdil, M., Horký, J., Mikl, M. & Seizure, R. K. Magnetic resonance spectroscopy of the thalamus in patients with typical absence epilepsy. *ElsevierD Fojtiková, M Brázdil, J Horký, M Mikl, R Kuba, P Krupa, I RektorSeizure, 2006•Elsevier* https://www.sciencedirect.com/science/article/pii/S1059131106001245 (2006).

176. Helms, G., Ciumas, C., Kyaga, S. & Savic, I. Increased thalamus levels of glutamate and glutamine (Glx) in patients with idiopathic generalised epilepsy. *J. Neurol. Neurosurg. Psychiatry* **77**, 489–494 (2006).

177. Haki, C., Gümüştaş, O. G., Bora, I., Gümüştaş, A. U. & Parlak, M. Proton magnetic resonance spectroscopy study of bilateral thalamus in juvenile myoclonic epilepsy. *Seizure* **16**, 287–295 (2007).

178. Lin, K. *et al.* Magnetic resonance spectroscopy reveals an epileptic network in juvenile myoclonic epilepsy. *Wiley Online LibraryK Lin, H Carrete Jr, J Lin, MM Peruchi, GM de Araújo Filho, MSB Guaranha, LMFF GuilhotoEpilepsia, 2009•Wiley Online Library* **50**, 1191–1200 (2009).

179. De Araújo Filho, G. M. *et al.* Are personality traits of juvenile myoclonic epilepsy related to frontal lobe dysfunctions? A proton MRS study. *Wiley Online LibraryGM de Araujo Filho, K Lin, J Lin, MM Peruchi, LOSF Caboclo, MSB GuaranhaEpilepsia, 2009•Wiley Online Library* **50**, 1201–1209 (2009).

180. Doelken, M. T. *et al.* Multi-voxel magnetic resonance spectroscopy at 3 T in patients with idiopathic generalised epilepsy. *Seizure* **19**, 485–492 (2010).

181. Hattingen, E. *et al.* Frontal and thalamic changes of GABA concentration indicate dysfunction of thalamofrontal networks in juvenile myoclonic epilepsy. *Epilepsia* **55**, 1030–1037 (2014).

182. Cevik, N. *et al.* Evaluation of cognitive functions of juvenile myoclonic epileptic patients by magnetic resonance spectroscopy and neuropsychiatric cognitive tests concurrently. *Neurol. Sci.* **37**, 623–627 (2016).

183. Abedi-Firouzjah, R. *et al.* Exploring Changes in Thalamus Metabolites as Diagnostic Biomarkers in Idiopathic Generalised Epilepsy Patients Using Magnetic Resonance Spectroscopy. *Malays. J. Med. Sci.* **27**, 78–86 (2020).

184. Daker, L. I. *et al.* Could thalamic biochemical changes correlate to cognitive impairment in idiopathic generalized epilepsy? *The Egyptian Journal of Neurology, Psychiatry and Neurosurgery 2023 59:1* **59**, 35- (2023).

185. Kabay, S. C., Gumustas, O. G., Karaman, H. O., Ozden, H. & Erdinc, O. A proton magnetic resonance spectroscopic study in juvenile absence epilepsy in early stages. *European Journal of Paediatric Neurology* **14**, 224–228 (2010).

186. Ristić, A. J. *et al.* Hippocampal metabolic dysfunction in juvenile myoclonic epilepsy: 3D multivoxel spectroscopy study. *J. Neurol. Sci.* **305**, 139–142 (2011).

187. Chowdhury, F. A. *et al.* Investigation of glutamine and GABA levels in patients with idiopathic generalized epilepsy using MEGAPRESS. *J. Magn. Reson. Imaging* **41**, 694–699 (2015).

188. Leite, C. da C., Valente, K. D. R., Fiore, L. A. & Otaduy, M. C. G. Proton spectroscopy of the thalamus in a homogeneous sample of patients with easy-to-control juvenile myoclonic epilepsy. *Radiol. Bras.* **50**, 279–284 (2017).

189. Chiappa, K. H., Hill, R. A., Huang-Hellinger, F. & Jenkins, B. G. Photosensitive epilepsy studied by functional magnetic resonance imaging and magnetic resonance spectroscopy. *Epilepsia* **40**, 3–7 (1999).

190. Hill, R. A., Chiappa, K. H., Huang-Hellinger, F. & Jenkins, B. G. Hemodynamic and metabolic aspects of photosensitive epilepsy revealed by functional magnetic resonance imaging and magnetic resonance spectroscopy. *Epilepsia* **40**, 912–920 (1999).

191. Yıldırım, F., Aydin, Z., Sakcı, Z. & Yalçın, A. D. Investigation of Patients With Eye Closure Sensitive Epilepsy With Magnetic Resonance Spectroscopy. *Clin. EEG Neurosci.* **53**, 45–53 (2022).

192. Aydin-Ozemir, Z., Terzibasioglu, E., Altindag, E., Sencer, S. & Baykan, B. Magnetic resonance spectroscopy findings in photosensitive idiopathic generalized epilepsy. *journals.sagepub.comZ Aydin-Ozemir, E Terzibasioglu, E Altindag, S Sencer, B BaykanClinical EEG and neuroscience, 2010•journals.sagepub.com* **41**, 42–49 (2010).

193. Kaczmarek, I., Michalska, J., Kociemba, W., Antczak, S. & Steinborn, B. Neurometabolic activity in the thalamic and frontal cortex and cognitive functions in adolescents with generalized epileptic syndromes. *Acta Neuropsychologica* **22**, 169–182 (2024).

194. Nakamura, Y. *et al.* Quantitative measurement of peritumoral concentrations of glutamate, N-acetyl aspartate, and lactate on magnetic resonance spectroscopy predicts glioblastoma-related refractory epilepsy. *Acta Neurochirurgica 2022 164:12* **164**, 3253–3266 (2022).

195. Hashiguchi, M. *et al.* Glutamic Acid and Total Creatine as Predictive Markers for Epilepsy in Glioblastoma by Using Magnetic Resonance Spectroscopy Before Surgery. *World Neurosurg.* **160**, e501–e510 (2022).
196. Ravishankar, D. & Sunil, D. PREDICTING EPILEPTOGENIC POTENTIAL OF BRAIN METASTASES BY GLUTAMATE ANALYSIS USING MAGNETIC RESONANCE SPECTROSCOPY: A RETROSPECTIVE STUDY. *Suranaree Journal of Science & Technology* **31**, 1 (2024).
197. Jayasekera, B. A. P. *et al.* Elevated glioma-related cortical glutamate in vivo is associated with ex vivo interictal discharges in human brain slices. *Brain Commun.* **7**, (2025).
198. Pascuzzo, R. *et al.* Glutamate to GABA ratio is elevated in patients with IDH-mutant lower-grade gliomas and seizures. *Neurooncol. Adv.* **7**, (2025).
199. Chernov, M. F. *et al.* Proton MRS of the peritumoral brain. *J. Neurol. Sci.* **228**, 137–142 (2005).
200. Nakae, S. *et al.* Association of preoperative seizures with tumor metabolites quantified by magnetic resonance spectroscopy in gliomas. *Scientific Reports 2021 11:1* **11**, 7927- (2021).
201. Nagashima, H. *et al.* Association between accumulation of 2-hydroxyglutarate detected by MR spectroscopy and preoperative seizure in IDH-mutant glioma. *J. Neurosurg.* **142**, 712–721 (2024).
202. Vuori, K. *et al.* Low-grade gliomas and focal cortical developmental malformations: differentiation with proton MR spectroscopy. *Radiology* **230**, 703–708 (2004).
203. Fellah, S. *et al.* Epileptogenic brain lesions in children: the added-value of combined diffusion imaging and proton MR spectroscopy to the presurgical differential diagnosis. *Childs Nerv. Syst.* **28**, 273–282 (2012).
204. Peeling, J. & Sutherland, G. 1H magnetic resonance spectroscopy of extracts of human epileptic neocortex and hippocampus. *Neurology* **43**, 589–594 (1993).
205. Holopainen, I. E. *et al.* Proton spectroscopy in children with epilepsy and febrile convulsions. *Pediatr. Neurol.* **19**, 93–99 (1998).
206. Seymour, K. J., Bluml, S., Sutherling, J., Sutherling, W. & Ross, B. D. Identification of cerebral acetone by 1H-MRS in patients with epilepsy controlled by ketogenic diet. *Magnetic Resonance Materials in Physics, Biology and Medicine* **8**, 33–42 (1999).
207. Tan, Z. *et al.* Alterations in Brain Metabolites in Patients with Epilepsy with Impaired Consciousness: A Case-Control Study of Interictal Multivoxel 1H-MRS Findings. *AJNR Am. J. Neuroradiol.* **40**, 245 (2019).
208. Simani, L. *et al.* Neurochemicals of limbic system and thalamofrontal cortical network: Are they different between patients with idiopathic generalized epilepsy and psychogenic nonepileptic seizure? *Epilepsy and Behavior* **112**, (2020).

209. Faheem, M. H., Dabour, A. S. & Abdelhaie, O. M. Diagnostic and prognostic role of proton single-voxel spectroscopy (SVS) in non-lesional epilepsy pediatric patients: prospective controlled study. *Egyptian Journal of Radiology and Nuclear Medicine 2020 51:1* **51**, 143- (2020).

210. Kilic, H. *et al.* Electrical status epilepticus in sleep: The role of thalamus in etiopathogenesis. *Seizure* **93**, 44–50 (2021).

211. Wang, L. *et al.* Abnormal metabolites in the dorsolateral prefrontal cortex of female epilepsy patients with migraine without aura. *Neuroreport* **35**, 1155–1162 (2024).

212. Rincon, S. P. *et al.* The Use of Magnetic Resonance Spectroscopy in the Evaluation of Pediatric Patients With Seizures. *Pediatr. Neurol.* **58**, 57–66 (2016).

213. Petroff, O. A. C., Hyder, F., Rothman, D. L. & Mattson, R. H. Homocarnosine and seizure control in juvenile myoclonic epilepsy and complex partial seizures. *Neurology* **56**, 709–715 (2001).

214. Simister, R. J., McLean, M. A., Barker, G. J. & Duncan, J. S. A proton magnetic resonance spectroscopy study of metabolites in the occipital lobes in epilepsy. *Epilepsia* **44**, 550–558 (2003).

215. Gonen, O. M. *et al.* Seven-tesla quantitative magnetic resonance spectroscopy of glutamate, γ-aminobutyric acid, and glutathione in the posterior cingulate cortex/precuneus in patients with epilepsy. *Epilepsia* **61**, 2785–2794 (2020).

216. Seyfert, S., Bernarding, J. & Braun, J. Volume-selective 1H MR spectroscopy for in vivo detection of valproate in patients with epilepsy. *Neuroradiology* **45**, 295–299 (2003).

217. Wang, Z. J. *et al.* In vivo measurement of brain metabolites using two-dimensional double-quantum MR spectroscopy—exploration of GABA levels in a ketogenic diet. *Magnetic Resonance in Medicine: An Official Journal of the International Society for Magnetic Resonance in Medicine* **49**, 615–619 (2003).

218. Simister, R. J., McLean, M. A., Barker, G. J. & Duncan, J. S. The effect of sodium valproate on proton MRS visible neurochemical concentrations. *Epilepsy Res.* **74**, 215–219 (2007).

219. Garcia, M. *et al.* Valproate-induced metabolic changes in patients with epilepsy: assessment with 1H-MRS. *freidok.uni-freiburg.de* **50**, 486–492 (2009).

220. Wright, J. N., Saneto, R. P. & Friedman, S. D. β-Hydroxybutyrate Detection with Proton MR Spectroscopy in Children with Drug-Resistant Epilepsy on the Ketogenic Diet. *AJNR Am. J. Neuroradiol.* **39**, 1336–1340 (2018).

221. Napolitano, A. *et al.* The Ketogenic Diet Increases In Vivo Glutathione Levels in Patients with Epilepsy. *Metabolites* **10**, 1–9 (2020).

222. Hugg, J. W. *et al.* Lateralization of human focal epilepsy by 31P magnetic resonance spectroscopic imaging. *Neurology* **42**, 2011–2018 (1992).

223. Nakamura, K., Asakura, T. & Yatsushiro, K. Neuroimaging: A Localized Metabolic Study of Epileptic Brains with “P-Chemical Shift Imaging. *Psychiatry Clin. Neurosci.* **46**, 467–469 (1992).
224. Kuzniecky, R., Elgavish, G. A., Hetherington, H. P., Evanochko, W. T. & Pohost, G. M. In vivo 31P nuclear magnetic resonance spectroscopy of human temporal lobe epilepsy. *Neurology* **42**, 1586–1590 (1992).
225. Laxer, K. D., Hubesch, B., Sappey-Marinier, D. & Weiner, M. W. Increased pH and seizure foci inorganic phosphate in temporal demonstrated by [31P] MRS. *Epilepsia* **33**, 618–623 (1992).
226. Garcia, P. A. *et al.* Phosphorus magnetic resonance spectroscopic imaging in patients with frontal lobe epilepsy. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society* **35**, 217–221 (1994).
227. van der Grond, J. *et al.* Regional distribution of interictal 31P metabolic changes in patients with temporal lobe epilepsy. *Epilepsia* **39**, 527–536 (1998).
228. Chu, W.-J. *et al.* Lateralization of human temporal lobe epilepsy by 31P NMR spectroscopic imaging at 4.1 T. *Neurology* **51**, 472–479 (1998).
229. Pan, J. W. *et al.* Regional energetic dysfunction in hippocampal epilepsy. *Acta Neurol. Scand.* **111**, 218–224 (2005).
230. Andrade, C. S. *et al.* Widespread pH abnormalities in patients with malformations of cortical development and epilepsy: A phosphorus-31 brain MR spectroscopy study. *Brain Dev.* **36**, 899–906 (2014).
231. Park, E. J. *et al.* Extratemporal abnormalities in phosphorus magnetic resonance spectroscopy of patients with mesial temporal sclerosis. *Arq. Neuropsiquiatr.* **74**, 93–98 (2016).
232. Ridley, B. *et al.* Brain sodium MRI in human epilepsy: Disturbances of ionic homeostasis reflect the organization of pathological regions. *Neuroimage* **157**, 173–183 (2017).
233. Azilinon, M. *et al.* Combining sodium MRI, proton MR spectroscopic imaging, and intracerebral EEG in epilepsy. *Hum. Brain Mapp.* **44**, 825–840 (2023).
234. Gauer, L. *et al.* Investigating sodium homeostasis of structural brain hubs in focal epilepsy using 7 T MRI. *Brain* **149**, 2139–2150 (2026).
235. Chu, W.-J. *et al.* Is the intracellular pH different from normal in the epileptic focus of patients with temporal lobe epilepsy? A sup 31 P NMR study. *Neurology* **47**, 756–760 (1996).
236. Obata, T. *et al.* Neural damage due to temporal lobe epilepsy: Dual-nuclei (proton and phosphorus) magnetic resonance spectroscopy study. *Psychiatry Clin. Neurosci.* **58**, 48–53 (2004).
237. Davis, K. A. *et al.* Glutamate imaging (GluCEST) lateralizes epileptic foci in nonlesional temporal lobe epilepsy. *Sci. Transl. Med.* **7**, (2015).
238. Neal, A. *et al.* Glutamate weighted imaging contrast in gliomas with 7 Tesla magnetic resonance imaging. *Neuroimage Clin.* **22**, (2019).

239. Hadar, P. N. *et al.* Volumetric glutamate imaging (GluCEST) using 7T MRI can lateralize nonlesional temporal lobe epilepsy: A preliminary study. *Brain Behav.* **11**, (2021).
240. Lucas, A. *et al.* Mapping hippocampal glutamate in mesial temporal lobe epilepsy with glutamate weighted CEST (GluCEST) imaging. *Hum. Brain Mapp.* **44**, 549–558 (2023).
241. Wang, K. *et al.* Lateralization of temporal lobe epileptic foci with automated chemical exchange saturation transfer measurements at 3 Tesla. *EBioMedicine* **89**, (2023).
242. Huang, Z. *et al.* Excitatory-inhibitory imbalance in temporal lobe epilepsy: a 5T multimodal MRI biomarker for focus localization and drug resistance stratification. *Front. Aging Neurosci.* **17**, 1660608 (2025).
243. Xu, D. *et al.* Hippocampal Glutamate Levels and Their Correlation With Subregion Volume in School-Aged Children With MRI-Negative Epilepsy: A Preliminary Study. *J. Magn. Reson. Imaging* **61**, 1258–1268 (2025).
244. Petroff, O. A. C., Errante, L. D., Rothman, D. L., Kim, J. H. & Spencer, D. D. Glutamate–glutamine cycling in the epileptic human hippocampus. *Epilepsia* **43**, 703–710 (2002).
245. Otsuki, T., Nakama, H., Kanamatsu, T. & Tsukada, Y. Glutamate metabolism in epilepsy: 13C-magnetic resonance spectroscopy observation in the human brain. *Neuroreport* **16**, 2057–2060 (2005).
246. Williamson, A., Patrylo, P. R., Pan, J., Spencer, D. D. & Hetherington, H. Correlations between granule cell physiology and bioenergetics in human temporal lobe epilepsy. *Brain* **128**, 1199–1208 (2005).
247. Ahmadian, N. *et al.* Detection of regional metabolic alteration using 7T deuterium metabolic imaging in MRI-negative, 18FDG-PET-positive epilepsy patients. *MAGMA* **39**, (2026).
248. Wagnerová, D. *et al.* The relationships between quantitative MR parameters in hippocampus in healthy subjects and patients with temporal lobe epilepsy. *Physiol. Res.* **64**, 407–417 (2015).
249. Vermathen, P., Laxer, K. D., Matson, G. B. & Weiner, M. W. Hippocampal structures: anteroposterior N-acetylaspartate differences in patients with epilepsy and control subjects as shown with proton MR spectroscopic imaging. *Radiology* **214**, 403–410 (2000).