Title: Detection of Neuroinflammation in MRI-Negative Drug-Resistant Epilepsy by Multiparametric Quantitative MRI

Running Title: Detection of Neuroinflammation in Epilepsy by MRI

Authors: Asieh Fatemidokht[1,*], Keyvan Hassanzadeh[2], Mohammad Hossein Harirchian[3], Mohammad Ali Oghabian[4], Abbas Tafakhori[4]

1. *Department of Radiology, Faculty of Allied Medical Sciences, Rafsanjan University of Medical Sciences, Rafsanjan, Iran.*
2. *Mojtaba Asadi Non-Profit Institute, Rafsanjan, Iran.*
3. *Iranian Center of Neurological Research, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran.*
4. *Department of Medical Physics and Biomedical Engineering, Tehran University of Medical Sciences, Tehran, Iran.*

***Corresponding Author**: Asieh Fatemidokht, Department of Radiology, Faculty of Allied Medical Sciences, Rafsanjan University of Medical Sciences, Rafsanjan, Iran. E-mail: a.fatemidokht@rums.ac.ir, a_fatemidokht@yahoo.com

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Abstract

Background: Approximately 30–40% of drug-resistant epilepsy (DRE) cases are MRI-negative, showing no visible lesions on conventional magnetic resonance imaging. This presents a significant challenge in localizing epileptic foci. However, recent evidence indicates that neuroinflammation plays a crucial role in epileptogenesis, offering potential biomarkers for more precise localization.

Purpose of the study: To evaluate whether multi-parametric quantitative MRI can detect neuroinflammation in the seizure-generating regions of patients with MRI-negative, drug-resistant epilepsy.

Methods: This study included twenty-one MRI-negative, drug-resistant epilepsy patients (mean age: 31.3 years) All participants underwent multi-parametric MRI at 1.5T, which included magnetization transfer imaging (MTI) and magnetic resonance spectroscopy (MRS). Regions of interest in epileptic patients were defined based on long-term video-EEG monitoring. Metabolite values from MRS and magnetization transfer ratios were analyzed using t-tests ($p < 0.05$) to compare normal and epileptic brain lobes in the patients.

Results: the analysis revealed significant metabolic and physiological alterations in epileptic regions. The magnetization transfer ratio (MTR) was significantly reduced in epileptic white matter (0.5718 ± 0.0141 vs. 0.5943 ± 0.0141, $p < 0.05$). Additionally, the myo-inositol to creatine ratio (mIns/Cr) was significantly elevated in epileptic areas (2.3581 ± 0.8257 vs. 1.7062 ± 0.4134, $p < 0.05$).

Conclusions: For patients with MRI-negative, drug-resistant epilepsy, multiparametric quantitative MRI provides a crucial tool for detecting neuroinflammation-related changes. By combining reduced magnetization transfer ratio (MTR) with increased myo-inositol to creatine (mIns/Cr) ratios, could provide helpful methods to localize epileptic focus and improve treatment in MRI-negative DRE.

Keywords: Drug-resistant epilepsy, neuroinflammation, magnetization transfer imaging, magnetic resonance spectroscopy, MRI-negative epilepsy

1. Introduction

Epilepsy, a highly prevalent chronic neurological disorder, affects approximately 1% of the global population(Zhang et al., 2023). Although more than 30 antiepileptic drugs (AEDs) are available, a substantial proportion (30–40%) of patients experience drug-resistant epilepsy (DRE), defined by the failure to achieve seizure freedom despite trials with at least two appropriately selected medications.(Beniczky et al., 2025; Kwan et al., 2010). Further complicating treatment, conventional MRI reveals no detectable lesions in about 20–40% of DRE cases, presenting significant challenges for identifying epileptic foci and guiding surgical interventions. (Zentner, 2020)

Over the past decade, the bidirectional relationship between neuroinflammation and epilepsy has gained increasing recognition(Dingledine et al., 2024; Vezzani, 2020) . Elevated neuroinflammation drives dysfunction in microglia and astrocytes, leading to neuronal hyperexcitability and excitotoxicity, and ultimately, seizures(Balosso et al., 2021; Shi et al., 2025).This inflammatory cascade involves various cytokines, chemokines, and complement factors that contribute to blood-brain barrier dysfunction, altered neurotransmitter balance, and modified synaptic transmission (Kamali et al., 2021; Meng & Yao, 2020)

Conventional MRI sequences often fail to detect subtle structural abnormalities associated with neuroinflammation in patients with drug-resistant epilepsy (DRE). (Yao et al., 2024) Human neuroimaging has significantly advanced the biological understanding of epilepsy, elucidating the relationships among pathophysiology, seizure management, and clinical outcomes. Recent developments have focused on quantitative MRI techniques.(Yoganathan et al., 2023) These advanced neuroimaging methods—including magnetization transfer imaging (MTI), magnetic resonance spectroscopy (MRS), and susceptibility-weighted imaging (SWI)—offer enhanced sensitivity to microstructural tissue changes linked to neuroinflammation .(Desale et al., 2024; Kung et al., 2023; Ranji-Burachaloo et al., 2019)

Magnetic Resonance Imaging (MRI) is a critical tool for diagnosing and managing epilepsy, particularly when surgical options are being considered.(Bernasconi & Bernasconi, 2022) Ongoing advancements in imaging techniques, using modalities to reveal changes during neuroinflammation in epileptic brain, show promise as non-invasive biomarkers which could significantly help the localization of epileptic regions in patients with drug-resistant epilepsy and without any abnormality in MRI images. Quantitative magnetization transfer and mIns/Cr are indirect biomarkers that may be associated with inflammation-related brain alterations, but they are not specific markers of neuroinflammation.(Harrison et al., 2015) However, our preliminary data indicate a statistically significant association between the levels of these biomarkers and neuroinflammation presence in epileptic region within our study population. Further research is warranted to precisely determine the sensitivity and specificity of these biomarkers in differentiating neuroinflammation from other disorders.

This study hypothesizes that multiparametric quantitative MRI (mp-qMRI), including magnetic resonance spectroscopy and magnetization transfer imaging, can detect neuroinflammation-related tissue changes in the epileptic regions of MRI-negative drug-resistant epilepsy (DRE) patients. Such findings would provide objective biomarkers and help to find focus location.

2. Materials and Methods

2.1 Participants

Participants in this prospective study included 21 patients with MRI-negative drug-resistant epilepsy (10 males, 11 females; mean age 31.3 ± 8.2 years, range 16–47 years), recruited from the Epilepsy Clinic at Imam Khomeini Hospital, Tehran, Iran. All patients met the International League Against Epilepsy (ILAE) criteria for drug-resistant epilepsy(Janmohamed et al., 2020; Löscher et al., 2020) had undergone comprehensive evaluations including long-term video-electroencephalography (LTM-VEEG) monitoring, and had conventional MRI studies confirmed negative for structural abnormalities by two experienced neuroradiologists. Table.1 shows demographic and clinical information of epileptic patients which include the sex, Age at onset(yr), Duration of seizure(yr) and EEG finding.

The study received approval from the institutional review board, and all participants provided written informed consent.

2.2 MRI Acquisition

MRI scans were performed using a 1.5-Tesla SIGNA scanner (GE Healthcare, Chicago, Illinois) equipped with an 8-channel phased-array head coil. The MRI scanner was better accessibility for participants and standardized acquisition protocols were applied to obtain images. The comprehensive multiparametric protocol included: Magnetization Transfer Imaging (MTI) was acquired using 2D spoiled gradient-echo sequences (TR/TE = 500/12 ms, flip angle = 20°, slice thickness = 5 mm, matrix = 256 × 256, FOV = 24 cm), both with and without magnetization transfer pulses. Magnetic Resonance Spectroscopy (MRS) was performed using a multi-voxel point-resolved spectroscopy (PRESS) sequence (TR/TE = 2000/35 ms, voxel size = 2 × 2 × 2 cm^3, NSA = 128), with multi voxel box placed on both normal and epileptic lobes which guided by VEEG monitoring.

2.3 Image Analysis

The imaging data were processed using three distinct analytical pipelines. For Magnetization Transfer Imaging (MTI), magnetization transfer ratio (MTR) maps were generated using the formula: MTR = [(M0 – MT) / M0] × 100%, where M0 represents the signal intensity without a magnetization transfer (MT) pulse, and MT represents the signal intensity with the MT pulse. It was clarified that ROI delineation was performed by two experienced neuroradiologists independently in white and gray matter regions corresponding to VEEG-identified epileptic regions and their contralateral homologous areas, and inter-rater reliability (ICC values 0.7) obtained. This addresses concerns regarding the reproducibility of manually defined ROIs. Magnetic Resonance Spectroscopy (MRS) spectral data were processed using TARQUIN software, which included manual quality control steps. This processing enabled the quantification of myo-inositol (mIns), creatine (Cr), and N-acetylaspartic acid (NAA) concentrations, with metabolite ratios subsequently calculated relative to creatine. Figure.1describes ROIs in (A) MTR

images and (B) Grid of multi-voxel ROI in epileptic and normal lobes in 19 yrs. MRI-negative refractory patients with temporal epilepsy.

2.4 Statistical Analysis

To analyze the data, MATLAB (MathWorks, Natick, MA) was used for all statistical computations. Group differences were assessed using two-tailed t-tests, with a significance threshold set at $p < 0.05$. Table.2 indicates the statistical measurements of MTR in white and gray matter and MRS metabolites in epileptic and normal lobes of patients. No multiple-comparison correction was applied. The data distribution was evaluated by fitting a Weibull distribution. The Weibull distribution was used as a descriptive tool to compare the overall shape of the group distributions; peak separation was interpreted as a visual aid rather than a formal test of statistical significance. Figure.2 and 3 evaluate statistically box plots and Weibull distribution of parameters with p-value<0.05 in healthy and epileptic lobes

3. Results

A significant reduction in Magnetization Transfer Ratio (MTR) values was observed in epileptic white matter regions (0.5718 ± 0.0141) compared to contralateral white matter (0.5943 ± 0.0141, $p < 0.05$). In contrast, gray matter MTR values did not differ significantly between epileptic (0.5234 ± 0.0519) and contralateral areas (0.5248 ± 0.0519, $p > 0.05$). The myo-inositol to creatine ratio (mIns/Cr) was significantly elevated in epileptic regions (2.36 ± 0.83) compared to contralateral regions (1.71 ± 0.41, $p < 0.05$). In contrast, NAA/Cr ratios exhibited a non-significant trend toward reduction. Table.2 demonstrates Statistical evaluation of the parameters specified in the epileptic and normal lobe of the patients. Figure.2 shows statistical evaluation by box plots of parameters with p-value<0.05 in healthy and epileptic lobes. Also figure.3 describes statistical evaluation by Weibull distribution curves of parameters with p-value<0.05 in healthy and epileptic lobes.

4. Discussion

This study demonstrates that multiparametric quantitative MRI can successfully detect neuroinflammation-related tissue changes in MRI-negative, drug-resistant epilepsy (DRE) patients. The combined findings of reduced magnetization transfer ratio (MTR)**,** and elevated myo-inositol/creatine (mIns/Cr) ratios constitute objective evidence of neuroinflammatory processes in epileptic regions.

Our observation of decreased MTR in epileptic white matter aligns with recent preclinical and human evidence showing network-specific myelination changes during the progression of generalized epilepsy. Using magnetization transfer and diffusion MRI–based g-ratio estimation, demonstrated that seizure activity drives myelin structural plasticity and microstructural damages in a regionally specific manner, particularly in the anterior corpus callosum (Kung et al., 2023; Sierra et al., 2015) . Such findings indicate that repeated epileptic discharges can alter myelin

integrity and axonal organization and could directly connect to inflammatory signals lead to axonal guidance molecules disruptions. (Liu et al., 2025). Studies highlighted the role of quantitative magnetization transfer imaging as a sensitive biomarker of microstructural alterations secondary to inflammation in central nervous system (CNS) disorders(Granziera et al., 2021; Harrison et al., 2015; Nwaubani et al., 2022). Consequently, the reduced MTR detected in our cohort likely reflects neuroinflammation-associated tissue changes, including myelin or macromolecular pool disruption, within MRI-negative epileptic regions.

The elevated mIns/Cr ratios observed in epileptic regions are consistent with glial activation and astrogliosis—hallmarks of neuroinflammatory processes. Myo-inositol serves as an osmolyte and metabolic marker of glial cells, with increased levels reflecting reactive astrocytosis commonly observed in inflammatory CNS conditions(Pimentel-Silva et al., 2020; Smucny et al., 2024) . In experimental models, transient or sustained rises in hippocampal myo-inositol correlate with astrogliosis and later epileptogenesis following status epilepticus and it serves as a significant biomarker of neuroinflammation(Kandashvili et al., 2022; Simonato et al., 2021) . Notably, such increases may predict which animals later develop spontaneous seizures, even when neuronal loss is similar, suggesting a predictive biomarker potential for myo-inositol. Recent systematic reviews also emphasize that inflammatory mediators—cytokines, microglial activation, and oxidative stress pathways—are central in the pathophysiology of DRE(Aguilar-Castillo et al., 2024) . Thus, our MRS-based findings may represent a noninvasive correlate of glial-driven neuroinflammation.

By integrating these multiparametric imaging biomarkers (MTR and mIns/Cr), we identified MTR and mIns/Cr as the most discriminative features for localizing epileptic foci. This result supports the emerging paradigm that multimodal imaging integration enhances sensitivity and specificity for detecting subtle epileptic lesions in MRI-negative patients(Wang et al., 2024). Combining structural, and metabolic provides a more holistic and quantitative assessment of inflammatory processes that remain invisible to conventional MRI sequences.

Limitations and Future Directions

Despite these encouraging findings, several limitations must be acknowledged. First, neither reduced MTR nor elevated mIns/Cr is entirely specific to neuroinflammation; both may be influenced by demyelination, osmotic shifts, medication, or aging. Longitudinal and multimodal validation studies—including TSPO-PET or histopathological correlation—are needed to confirm specificity. Second, The relatively small sample size (n=21) limits statistical power and generalizability. We have added this as an explicit limitation and clarified that our conclusions are restricted to **within-cohort associations** rather than causal effects or between-group comparisons. Also, no correction for multiple comparisons was applied in the original analysis, and this should be explicitly recognized as a limitation. The 1.5-Tesla field strength, while adequate for clinical imaging, may limit sensitivity compared to higher field strengths. Future studies should investigate these findings at 3T or ultra-high-field MRI systems. Additionally, validation in larger, multicenter cohorts is needed to establish clinical utility. Effect sizes were not calculated in the present analysis, and future studies should report them to better quantify the magnitude and clinical relevance of the observed effects. Finally, while machine-learning integration improves discrimination, external validation in larger multicentric datasets is essential to ensure generalizability.

Clinical and Translational Implications

Our findings highlight the clinical potential of advanced quantitative MRI biomarkers in MRI-negative DRE. These biomarkers can facilitate noninvasive detection of neuroinflammation-driven epileptic substrates, improve individualized presurgical localization, and provide quantitative markers for disease monitoring or therapeutic response. The integration of imaging and molecular biomarkers—such as cytokine profiling or transcriptomic markers—could yield a precision-medicine framework for epilepsy management and future immunomodulatory trials.

5. Conclusions

Multiparametric quantitative MRI successfully detects neuroinflammation-related changes in MRI-negative drug-resistant epilepsy patients. The combination of magnetization transfer imaging and magnetic resonance spectroscopy, provides complementary information about tissue microstructure, and metabolism in epileptic regions. These findings support the presence of neuroinflammation in epileptic region and offer potential biomarkers for improving localization and treatment of MRI-negative DRE. It is noted cause no healthy control group was included, the present findings should be interpreted as within-cohort associations rather than evidence of disease-specific or causal effects

Future research should focus on validating these biomarkers in larger cohorts, investigating their relationship with surgical outcomes, and exploring their potential as therapeutic targets. The integration of advanced quantitative MRI techniques with artificial intelligence approaches holds promise for personalized epilepsy care.

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Footnotes

Conflict of Interests: No conflict of interests was declared. Ethical Approval:

Ethics code: IR.TUMS.MEDICINE.REC.1396.2662

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Patient Consent: Informed written consent was obtained from all patients for participating in this study and using their imaging data.

Data Availability Statement

Research data are available upon reasonable request to the corresponding author, subject to institutional review board approval and data sharing agreements.

Authors Contribution:

A.F: draft Manuscript, M.H.H and A.T: Help in collecting patients, M.O: supervision of Data

K.H: prepare images and tables, edit the paper

Highlights:

Detection inflammation in MRI-negative resistant epilepsy

Show brain metabolite changes due to neuroinflammation in epileptic brain

Show brain microstructural changes due to neuroinflammation in epileptic brain

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Table.1: Demographic and clinical information of MRI-negative DRE epileptic patients

subject	*Age(yr)*	*sex*	*Age at onset(yr)*	*Duration of seizure(yr)*	*EEG finding*
1	**19**	**M**	**10**	**9**	**Left Temporal**
2	**28**	**M**	**24**	**4**	**Left Frontal**
3	**47**	**F**	**13**	**34**	**Right Temporal**
4	**31**	**F**	**7**	**24**	**Left Temporal**
5	**20**	**M**	**9**	**11**	**Right Temporal**
6	**34**	**F**	**13**	**21**	**Right Temporal**
7	**34**	**F**	**4**	**30**	**Right Temporal**
8	**27**	**M**	**3**	**24**	**Right Frontal**
9	**41**	**F**	**10**	**31**	**Right Frontal**
10	**26**	**M**	**infancy**	**26**	**Right Temporal**
11	**33**	**F**	**7**	**26**	**Right Temporal**
12	**20**	**F**	**9**	**11**	**Right Occipital**
13	**46**	**M**	**25**	**21**	**Right Temporal**
14	**17**	**M**	**12**	**5**	**Right Frontal**
15	**26**	**F**	**15**	**11**	**Right temporal**
16	**47**	**F**	**27**	**20**	**Right temporal**
17	**45**	**F**	**15**	**30**	**Right frontal**
18	**17**	**M**	**12**	**5**	**Right frontal**
19	**21**	**M**	**17**	**4**	**Left temporal**
20	**16**	**M**	**10**	**6**	**Right temporal**
21	**40**	**F**	**30**	**10**	**Left temporal**

Table.2: Statistical measurements of the MTR in white and gray matter and MRS metabolites specified in the epileptic and normal lobe of the patient (* p-value <0.05)

Trait		Epileptic		Normal		p-value	t-test data
		Mean	Standard deviation	Mean	Standard deviation		
MTR	WM	0.5718	0.0141	0.5943	0.0141	0.0005*	-3.93
	GM	0.5234	0.0519	0.5248	0.0374	0.93	-0.08
MRS	Cr	3.5511	2.0936	3.8398	2.1390	0.72	-0.36
	Ins	8.3873	5.9945	6.8198	5.5802	0.48	0.71
	NAA	6.0851	1.5357	6.7892	2.2626	0.34	-0.96
	Ins/Cr	2.3581	0.8257	1.7062	0.4134	0.02*	2.64
	NAA/Cr	1.9522	0.2386	1.9817	0.2854	0.88	-0.15

Figure.1: An example of manually drawn ROIs in (A) MTR images, (B) Grid of multi-voxel ROI in epileptic and normal lobes in a 19(Yrs) MRI-negative refractory patients with temporal epileptic lobe verified by VEEG.

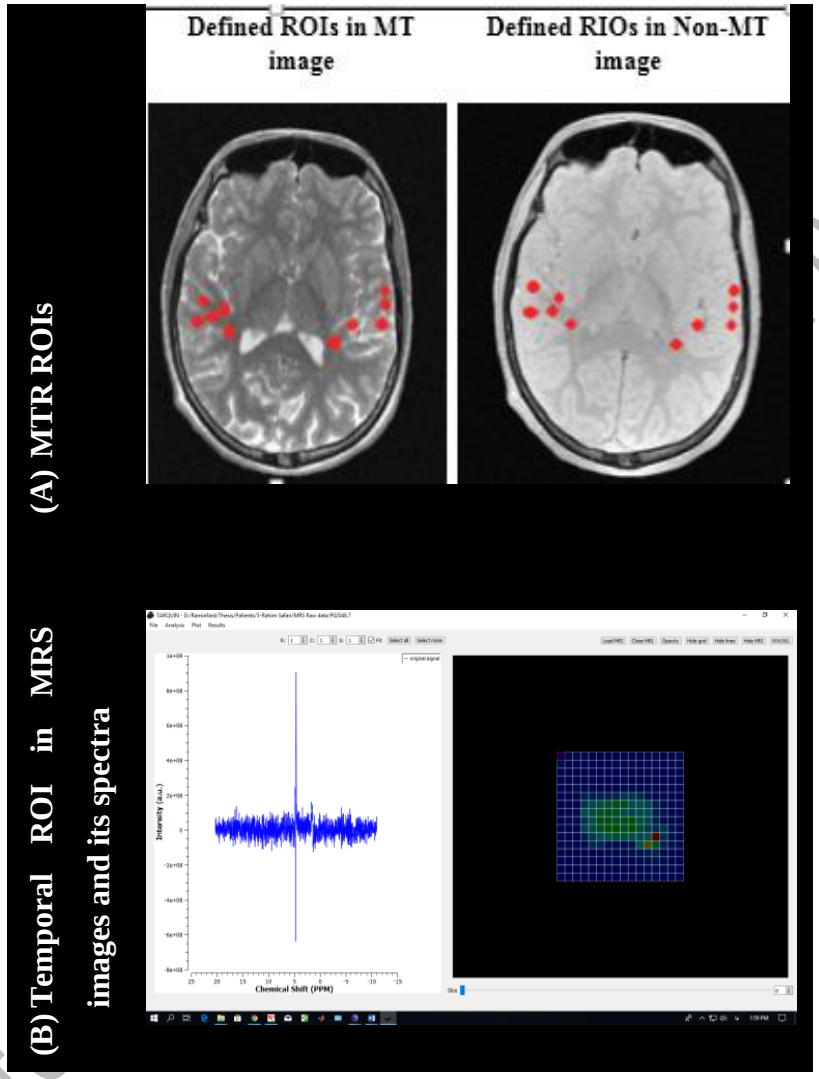
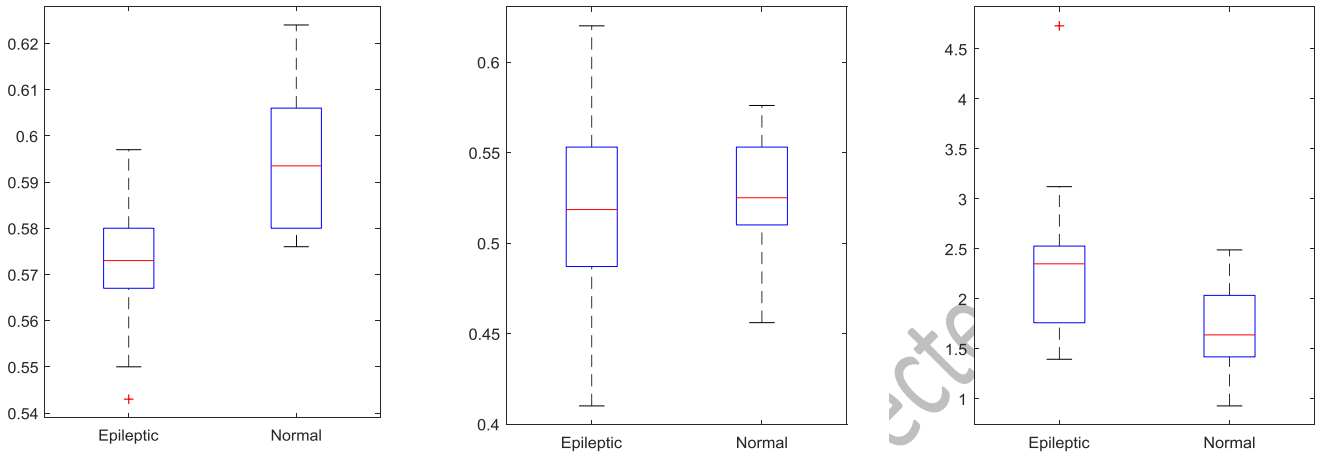
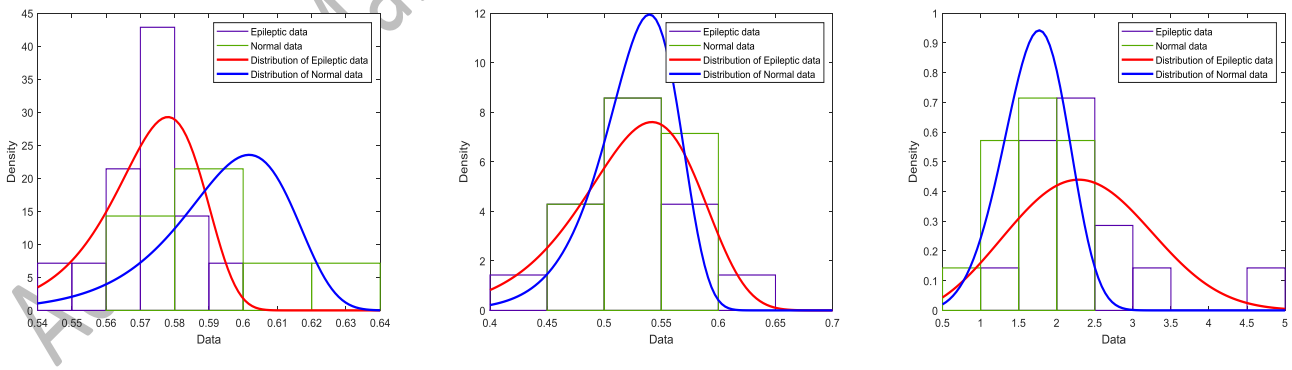


Figure.2: Statistical evaluation by box plots of (A) MTR in white matter, (B) MTR in Gray matter and (C) Myo-Ins/Cr with p-value<0.05 in healthy and epileptic lobes.



(A)MTR-WM **(B)MTR-GM** **(C)Myo-Ins/Cr**

Figure.3: Statistical evaluation by Weibull distribution curves of (A) MTR in white matter, (B) MTR in Gray matter and (C) Myo-Ins/Cr with p-value<0.05 in healthy and epileptic lobes



(A)MTR-WM **(B)MTR-GM** **(C)Myo-Ins/Cr**