ORIGINAL ARTICLE

Utilising MRI Data and VOI-Based Analysis for Enhanced Epilepsy Prediction: A Translational Approach from Bench to Bedside

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ABSTRACT

Background: Epilepsy is one of the most prevalent neurological disorders globally, profoundly impacting patient's quality of life and stretching healthcare resources. Despite technological advances in neuroimaging, early and accurate detection of epileptic foci remains elusive, especially when standard MRI scans appear structurally normal. For clinicians, radiologists and neurologists, the limitations of subjective interpretation underscore an urgent need for objective diagnostic methods. This study addresses that gap by introducing Volume of Interest (VOI)-based analysis as an innovative tool to detect microstructural brain abnormalities associated with epilepsy. **Methods:** This study involves a retrospective analysis of 30 brain MRI images (T1-Weighted MPRAGE), comprising of 12 epilepsy patients and 18 matched controls (11 males, 19 females; mean age 42.7 ± 17.2 years). The images were converted from the DICOM format into the Brain Imaging Data Structures (BIDS) standard using the fMRIPrep platform, which were then normalised following the standard Montreal Neurological Institute (MNI) template. The images were segmented into Grey Matter, White Matter and Cerebrospinal Fluid. The segmented Grey Matter regions have then been analysed using VOI-based analysis from the Harvard-Oxford Cortical Structural Atlas. The VOI-based analysis results were then statistically tested using ANCOVA with False Detection Rate (FDR) correction. **Results:** Three regions show statistically significant ANCOVA results, which were Superior Frontal Gyrus (p=0.041), Superior Parietal Lobule (p=0.026) and Lingual Gyrus (p=0.036). However, all three regions fail the FDR correction (q=0.36). **Conclusion:** This work shows that combining MRI data with VOI-based analysis can reveal subtle structural patterns in the superior frontal gyrus, superior parietal lobule and lingual gyrus that may contribute to the understanding of epilepsy risk. Although these patterns were not sustained after FDR correction, they offer a promising direction for more objective predictive tools. Continued research with larger cohorts is essential to confirm these early signals and strengthen their relevance for epilepsy prediction.

INTRODUCTION

Epilepsy is a long-standing neurological condition marked by recurrent, unprovoked seizures that can affect many aspects of a person's life. With an estimated 50 million people affected globally, the disorder continues to place a significant burden on individuals, families and healthcare systems (World Health Organisation, 2023; Beghi, 2020). In Malaysia, the prevalence has been estimated at 7.8 cases per 1,000 people, reflecting a substantial public health concern (Fong et al., 2021). Certain groups such as younger adults, males and individuals with focal epilepsy or poorly controlled seizures remain at higher risk of complications, including Sudden Unexpected Death in Epilepsy (SUDEP) (Khor et al, 2021; 2022). These factors highlight the continuing need to improve the tools used for early detection and accurate diagnosis.

Magnetic Resonance Imaging (MRI) plays a central role in evaluating epilepsy, providing essential structural information that informs diagnosis and treatment planning. While advanced MRI technologies hold great potential, clinical interpretation still relies heavily on qualitative assessment, and subtle abnormalities can easily go unnoticed (Bernasconi et al., 2019).

Recent studies have shown that combining structural MRI with computational analysis can markedly improve diagnostic accuracy; for example, machine learning approaches such as Support Vector Machines (SVM) have achieved up to 94% accuracy in distinguishing epileptic from non-epileptic scans (Jamaludin al., 2022). These

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findings suggest that data-driven methods may help capture features that traditional visual diagnosis may miss, particularly in focal epilepsy where small structural variations may influence treatment decisions (Caldairou et al., 2022; Bank et al., 2023). Fractal analysis has gained attention in neuroimaging for its ability to quantify structural complexity within the brain. By estimating Fractal Dimension (FD), researchers can detect subtle changes in grey matter structures that may not be apparent on the routine scans (Gleichgerrcht et al., 2021; Ziukelis et al., 2022). This type of quantitative assessment offers an objective way to characterise brain morphology and has shown promise in various neurological conditions.

More recently, local or regional assessment such as Volume of Interest (VOI)-based analysis, has been used to identify fine-detailed structural differences across specific brain regions. Studies have demonstrated the effectiveness of this approach in detecting intricate neuroanatomical variations linked to cognitive and neurological traits (Jamaludin et al., 2022). Applying VOI-based analysis to epilepsy may therefore offer a powerful extension to conventional MRI interpretation by capturing regional patterns associated with the condition.

Although quantitative imaging methods are gaining traction, the potential of VOI-based analysis for predicting epilepsy remains largely unexplored. Current diagnostic practices still depend heavily on subjective MRI interpretation, which may overlook the subtle microstructural changes that characterise epileptogenic brain tissues. Bridging this gap is important for improving diagnostic reliability and for advancing objective, image-based markers of epilepsy. In response, this study aimed to determine whether an automated, atlas-based VOI volumetric pipeline applied to high-resolution T1-weighted MRI of brain can discriminate patients with epilepsy from healthy controls. Through these objectives, the study seeks to contribute to a more rigorous and objective approach to epilepsy prediction using structural MRI.

MATERIALS AND METHODS

Study Design and Data Overview

This study was conducted using a retrospective design involving structural brain MRI scans obtained from the Department of Radiology, Sultan Ahmad Shah Medical Centre (SASMEC @IIUM). Three ethical clearances were obtained; 1) Kulliyyah Postgraduate and Research Committee (KPGRC) (ID Number: KAHS 40/25), 2) IIUM Research Ethical Committee (IREC) (IREC Number: IREC 2025-086) and 3) SASMEC @IIUM Research Committee (SASRC) (Reference Number: IIUM/423/013/14/1/SRG25-072-0072).

MRI Acquisition

The MRI system used was 3 Tesla Siemens Magnetom Spectra Scanner (Siemens Medical Solutions, Erlangen, Germany). Its gradient strength is 33 mT/m with slew rate of 125 T/m/s. The standard T1-Weighted 3D-MPRAGE (3D-Magnetisation Prepared Rapid Gradient Echo) protocol was used, with TR value of 1880 ms, TE of 3 ms and TA of 4.23 minute. The voxel size of 1.0 mm x 1.0 mm x 1.0 mm was used, with the FoV in the read direction of 250 mm. The slice thickness during acquisition was set at 45.5% where the phase encoding was set from right part of the brain to the left direction. The number of slices per image slab was 176. The raw imaging data were originally stored in native Digital Imaging and Communication in Medicine (DICOM) format within clinical archives.

A total of thirty T1-weighted MPRAGE brain MRI images from the scans conducted between the year 2020 until 2024 were retrieved, representing twelve patients clinically diagnosed with epilepsy (confirmed by EEG test results) and eighteen matched healthy controls (11 males, 19 females; mean age 42.7 ± 17.2 years). The inclusion criteria are epilepsy patients diagnosed based on clinical history, EEG, and MRI results for epilepsy group, while healthy controls were confirmed with no history of neurological disorders by radiologist and neurologist. Age for both groups were 18 to 60 years old, for both male and female. Patients with comorbid neurological conditions (e.g., stroke, dementia). MRI contraindications (e.g., metal implants) and active pregnancy were excluded from this study. Both groups were matched for age and gender. The sample size was determined using the Power and Sample Size Program, guided by parameters published by Chang et al. (2023), and all eligible cases in the archive were used for this retrospective study.

Preprocessing Pipeline

Image conversion and preparation

The raw imaging data were originally stored in native Digital Imaging and Communication in Medicine (DICOM) format within clinical archives. To ensure a uniform data structure suitable for automated neuroimaging pipelines, the scans were converted into the Brain Imaging Data Structure (BIDS) standard. This conversion was facilitated by a custom workflow built around the script *dcm_to_mni.py*, which systematically detected DICOM series for each subject and executed conversion using *heudiconv*. The script first attempted the standard *reproin* heuristic to identify the T1-weighted anatomical series. In

instances where this approach did not create BIDS-compliant directory structure, a fallback custom heuristic routed the MPRAGE sequence into the appropriate anatomical folder within the BIDS hierarchy. The resulting dataset conformed to the BIDS specification, with each participant assigned a unique subject identifier located within a cleanly organised directory structure.

Spatial Normalisation

All BIDS datasets were subsequently processed using the fMRIPrep platform, with additional preprocessing steps orchestrated via *dcm_to_mni.py*. Each subject's T1-weighted image was skull-stripped, bias-field corrected, and spatially normalised to the MNI152NLin2009cAsym template at 1-mm isotropic resolution. fMRIPrep also produced tissue probability maps for grey matter, white matter and cerebrospinal fluid. These outputs formed the foundation for the study's volumetric analysis, which focused on the extraction of both global tissue estimates and region-specific grey-matter volumes.

Tissue segmentation

Tissue segmentation was performed automatically through fMRIPrep's anatomical workflow. Grey matter, white matter and cerebrospinal fluid volumes were estimated by summing voxel-wise tissue probabilities, allowing the computation of global tissue measures expressed in millilitres. Total intracranial volume was estimated as the sum of the grey matter, white matter and cerebrospinal fluid; and was later included as a covariate in the group-comparison analysis.

VOI-Based Regional Analysis

Regional morphometric analysis was conducted using a VOI-based framework implemented in *analyse_VOI_HO.py*. This process involved integrating the Harvard-Oxford Cortical Structural Atlas with the grey-matter probability maps produced by fMRIPrep. For each subject, the atlas was resampled to match the individual's grey-matter anatomical space, ensuring spatial correspondence between atlas labels and tissue probabilities. Regional volumes were calculated by applying atlas-defined masks to the grey-matter probability maps and converting the resulting weighted sums into millilitres measurements. The script generated a consolidated dataset containing demographic information, global tissue measurements and regional VOI-based grey-matter volumes for all subjects.

This automated framework supports a repeatable, objective, and clinically transferable neuroimaging pipeline, integrating standardised conversion, robust preprocessing, and rigorous analysis to advance MRI-based biomarkers for more accurate epilepsy diagnosis.

Statistical Analysis

To assess neuroanatomical differences between epilepsy and control groups, an Analysis of Covariance (ANCOVA) was performed for each global and regional volume, using Statistical Package for the Social Sciences (SPSS) version 29. The models incorporated age and intracranial volume as covariates to account for inherent biological variability. Group differences were evaluated using ANOVA-derived F statistics extracted from each model. Given the large number of atlas-derived regions analysed, the Benjamini-Hochberg False Discovery Rate (FDR) correction was applied to adjust for multiple comparisons. Regions meeting an adjusted significance threshold of $q<0.05$ were considered to show statistically robust volumetric differences between groups.

This study presents a fully automated structural MRI pipeline designed to characterise epilepsy-related neuroanatomical differences from T1-weighted images (Figure 1). The workflow standardises preprocessing and segmentation to generate MNI-normalised images and tissue probability maps, enabling consistent extraction of atlas-based regional grey-matter volumes. These volumetric biomarkers are then compared between groups using ANCOVA with FDR correction. Overall, the pipeline supports transparent, reproducible analysis with potential for translation into routine neuroimaging workflows.

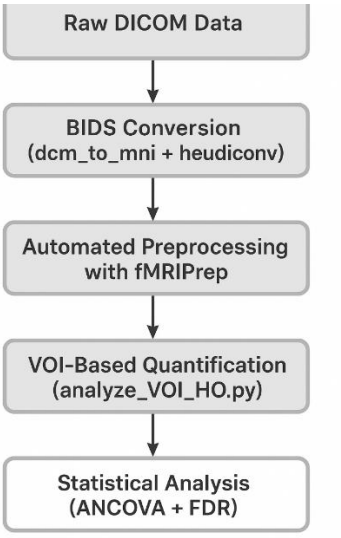

Figure 1: Automated T1-weighted MRI workflow: DICOM→BIDS (*heudiconv*), preprocessing with *fMRIPrep* (MNI-space outputs, tissue maps), Harvard–Oxford atlas grey-matter volumetry, and group comparison using ANCOVA with FDR correction.

RESULTS

Demographic Characteristics and Data Pre-Processing

This study used retrospective MRI brain images data from 30 participants, comprising of 12 individuals diagnosed with epilepsy and 18 age- and gender-matched healthy control subjects. The overall demographic profile indicated a mean age of 42.7 ± 17.2 years and a gender distribution of 11 males and 19 females.

High-resolution T1-weighted MPRAGE structural MRI sequences were acquired and utilised for all subsequent morphometric analysis. Data preparation involved a rigorous and reproducible pipeline: images were first converted from the DICOM format to the BIDS standard using the fMRIPrep platform. These data were subsequently normalised to the standard MNI template space. Following normalisation, images were meticulously segmented into grey matter, white matter and cerebrospinal fluid. Grey matter volume (GMV) were then derived using a VOI-based analysis across all 48 predefined cortical regions outlined by the Harvard-Oxford Cortical Structural Atlas.

Analysis of Covariance (ANCOVA) Findings (Uncorrected)

ANCOVA was used to statistically evaluate the inter-group differences in regional grey matter volume, adjusting for age and total intracranial volume (TIV) as covariates to mitigate potential confounding effects. Gender was excluded from the covariates as the images were retrieved retrospectively, and the limitation in getting the large number of images during the data collection process.

The initial inferential analysis performed using an uncorrected significance threshold of $p<0.05$, identified three specific cortical regions that exhibited a statistically significant volume alteration in the epilepsy group compared to controls. In all three regions, the epilepsy group demonstrated a reduced mean grey matter volume. The statistical details of these uncorrected findings are summarised in Table 1.

Table 1: Cortical VOIs showing statistically significant differences in grey matter volume between the epilepsy and control group using an uncorrected threshold ($p<0.05$).

Region	Mean (Epilepsy)	Mean (Control)	Difference	p-value
Superior Parietal Lobule	0.6791	0.6791	0.621	0.026
Lingual Gyrus	0.3798	0.3798	0.267	0.036
Superior Frontal Gyrus	0.2326	0.2326	0.093	0.041

Correction for Multiple Comparisons

Given the high number of concurrent statistical tests (n=48) performed across the anatomical atlas, the False Discovery Rate (FDR) method was applied to the entire p-value distribution to control the expected proportion of false positive findings (Type 1 errors).

Critically, following FDR control for multiple comparisons, no cortical VOI maintained a statistically significant difference at the controlled threshold of $q < 0.05$. Table 2 presents the comparison between the uncorrected p-values and the resulting FDR-corrected 1-values for the three regions identified in the initial analysis.

Table 2: q=FDR-corrected p-value for regions identified in the uncorrected ANCOVA analysis. No region met the significance threshold after controlling the False Discovery Rate across all 48 VOI tests.

Region	Corrected q-value (*FDR)	Partial η^2	**95% CI for Partial η^2
Superior Parietal Lobule	0.36	0.089	0.000 to > 1.0
Lingual Gyrus	0.48	0.094	0.000 to > 1.0
Superior Frontal Gyrus	0.51	0.106	0.000 to > 1.0

*FDR: False Discovery Rate

** Note: Upper confidence limits for Partial η^2 are unbounded due to the properties of the noncentral F distribution at moderate F values and sample size.

The comparison of the VOI-based values between the epilepsy and control groups showed small but detectable effects across the three regions of interest (ROIs). For the Superior Parietal Lobule, the group difference yielded $F(1,48) = 4.6938$ with a corresponding partial η^2 of 0.089. For the Lingual Gyrus, the analysis produced $F(1,48) = 4.9816$ and a partial η^2 of 0.094. For the Superior Frontal Gyrus, the observed effect was $F(1,48) = 5.7179$, reflecting a partial η^2 of 0.106.

The 95% confidence intervals (CIs) for partial η^2 showed lower bounds approximating 0.000 for all three ROIs, while the upper bounds were unbounded. This is a known consequence of inverting the noncentral F distribution in situations with modest F values and moderate sample sizes. The unbounded upper interval does not represent a computational error but reflects the limited precision with which the true effect size can be estimated. These findings collectively indicate the presence of small but meaningful regional differences despite the modest effect magnitudes.

This result confirms that while the three identified regions demonstrated a suggestive but not statistically robust after correction, the observed effect sizes were insufficient to pass the critical threshold necessary to declare a robust,

statistically independent difference when controlling for the large number of simultaneous comparisons.

DISCUSSION

This study set out to explore whether a fully automated, VOI-based morphometric analysis of high-resolution T1-weighted (MPRAGE) MRI could reliably detect subtle regional grey matter volume (GMV) differences between adults with epilepsy and matched healthy controls. While initial uncorrected analysis suggested reduced GMV in three cortical regions among epilepsy patients, these findings did not survive correction for multiple comparisons, highlighting both the promise and the current limitations of this approach. Thus, we did not identify robust volumetric biomarkers of epilepsy using this VOI-based approach in this modest sample.

The challenge of identifying robust, statistically significant regional brain abnormalities in epilepsy, especially in MRI-negative or nonlesional cases, is well documented in the literature. Recent studies have shown that advanced morphometric techniques, such as voxel-based and surface-based morphometry, can reveal subtle structural changes in both focal and generalised epilepsy, but their sensitivity and specificity are highly variable and often depend on sample size, imaging quality and analytic rigour (Bunyamin et al., 2025; Feng et al., 2025; Di Micco et al., 2025; Yang et al., 2024). For example, a large-scale study using the morphometric analysis program (MAP) in truly MRI-negative focal epilepsy found that, while MAP could detect previously overlooked lesions in a minority of cases, the overall diagnostic yield was limited, with a high rate of false positives and modest balanced accuracy (51-60%)(Feng et al., 2025). Similarly, a recent review emphasised that, although post-processing methods can convert some MRI-negative cases to MRI-positive, the concordance with true epileptogenic zones remains inconsistent, and integration with electrophysiological data is often necessary for clinical decision-making (Bunyamin et al., 2025).

The present findings are consistent with these reports, underscoring the complexity of epilepsy as a network disorder. Structural changes may be subtle, distributed, or below the threshold of detection for current morphometric pipelines, especially in small or heterogeneous groups. Notably, studies in temporal lobe epilepsy and idiopathic generalised epilepsy have demonstrated that GMV alterations often extend beyond the primary epileptogenic focus, involving widespread cortical and subcortical networks (Huang et al., 2025; Jber et al., 2021). However, the effect sizes are frequently modest, and robust group differences may only emerge in larger, multi-centre studies or when combined with other imaging modalities such as PET or advanced radiomics (Zhang et al., 2025; Tsai et al., 2025).

Recent advances in machine learning and radiomics have shown promise in improving the detection and prediction of epilepsy-related brain changes, particularly when integrating multiple imaging features and clinical data (Tsai et al., 2025; Yang et al., 2024). For instance, automated ROI-based morphometric features combined with machine learning have achieved high accuracy in distinguishing temporal lobe epilepsy from controls, even in MRI-negative cases (Yang et al., 2024). However, these approaches require large, well-annotated datasets and careful validation to avoid overfitting and ensure generalisability.

CONCLUSION

In summary, this study demonstrates the feasibility and reproducibility of a fully automated, VOI-based morphometric MRI analysis pipeline for investigating regional brain morphology in epilepsy. While initial findings suggested trends toward reduced grey matter volume in specific cortical regions among epilepsy patients, these differences did not reach statistical significance after correction for multiple comparisons. Consistent with current literatures, these findings are best interpreted as a methodological contribution, demonstrating the practical implementation and application of a fully automated, reproducible volumetric pipeline within a retrospective epilepsy cohort. (Bunyamin et al., 2025; Fearns et al., 2023; Di Micco et al., 2025; Yang et al., 2024).

The results underscore the need for larger, multi-centre studies, integration of multi-modal imaging (e.g., PET/MRI, radiomics), and the development of advanced analytic techniques to enhance sensitivity and specificity. Future research should also consider combining structural imaging with electrophysiological and clinical data to improve the localisation and characterisation of epileptogenic zones (Bunyamin et al., 2025; Feng et al., 2025; Yang et al., 2024). Ultimately, while VOI-based morphometric analysis holds promise as an objective, reproducible tool for epilepsy research and potentially for clinical practice, its current diagnostic utility remains limited in small, heterogeneous groups. Ongoing methodological refinement and collaborative research will be essential to realise its full potential in the early and accurate detection of epilepsy-related brain abnormalities.

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Declaration of Generative AI and AI-Assisted Technologies in the Writing Process

Artificial intelligence was used to improve content development and editing in the preparation of this manuscript. The authors subsequently reviewed, revised and approved all content and accept all responsibility for the final manuscript, and the authors guarantee its integrity and accuracy.

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