**Peer Review File**

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**Reviewer A**

The authors present a narrative review of various MRI sequences both from a historic perspective as well as more modern techniques. Furthermore, they describe the newer tools including AI and show their promise in detecting epileptogenic lesions. The authors need to make a distinction about surgery for lesions vs non lesional epilepsy. The fact is, non lesions epilepsy exists and our understanding of epilepsy and surgical intervention is incorporating a network based approach, especially in the field of neuromodulation. MRI remains one imaging technique in the armamentarium of the epileptologist and surgeon, but it doesn't provide an answer or culprit for seizures in many patients.

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**Reply:** added some data as suggested, please check pages 2-3, lines 58-66.

**Reviewer B**

In this manuscript entitled “Advances in MRI for the assessment of paediatric focal epilepsy: A narrative review,” the Authors aimed to provide the reader with a comprehensive evaluation of neuroimaging techniques improving the detection of epileptogenic lesions in the pediatric population.

PROS:
- Accurate lesion detection and characterization in children with lesional drug-resistant epilepsy correlate directly with post-surgical outcome. Hence, the paper deals with an important topic.

CONS:
- In the current version, it is hard to understand the clinical relevance of the radiological correlates.

General Comment:
- The review deals with an engaging and challenging topic, positively apprised by clinicians. Hence, discussing the tumultuous improvements of MRI in the last decades and the foreseeable application of newer sequences is of central importance. However, this review is generalist, failing to address any readership. Firstly, the challenges encountered in diagnosing children with focal drug-resistant epilepsy were not adequately detailed. Secondly, focal cortical dysplasia seems the review’s primary focus. Thirdly, it does satisfactorily answer the following question: ”Besides structural sequences, which sequence/AI tool gives additional information in specific etiologies?”. Lastly, the review stresses the technical part of sequences, taking some radiological concepts for granted (e.g., phase, readout, etc. ). A clinical readership may not be

familiar with these concepts. Please expand the review to attract the clinical readership, providing pieces of evidence on the clinical relevance of each sequence.

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**Reply**: we added some information, please check: page 2 lines 48-52; page 3 lines 67-78

Abstract

- In my opinion, the abstract has some flaws:

1) Introduces the global prevalence of epilepsy. However, epilepsy incidence peaks at younger and older ages. This information should be included in the abstract.

2) The abstract then focuses its attention on MRI-negative cases, which are only a limited subset of pediatric focal drug-resistant epilepsy. This overlooks the complexity of correctly discriminating between LEAT and FCD or localizing active tubers in children with tuberous sclerosis.

3) Why were some sequences defined while others were not?

4) Overall, the conclusions of the abstract tend to be pessimistic. However, in the last decades, neuroradiological and improved neurosurgical techniques have increased surgical candidacy. Also, international groups are sharing their databases, and several new sequences await to test their potential. The future for neuroimaging and children with lesional drug-resistant epilepsy seems brighter than before.

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**Reply 1**: added some data, please check page 2, line 35-36

**Reply 2**: added a broader list of references including LEAT and TSC, please check: page 7, lines 189-190; page 8, lines 219-223, pages 8-9, lines 224-236, page 9, lines 248-249.

**Reply 3**: added definition of missing sequences, please check: pages 8-9, lines 219-236.

**Reply 4**: changed the conclusions as suggested, please check conclusions in abstract (pages 1-2, lines 21-26) and final conclusions (pages 15-16, lines 391-403.

Introduction

- Please stress the concept that epilepsy diagnosis is based on the presence of unprovoked seizures. Also, please narrow your cohort to the pediatric population (see abstract comment 1).

- I suggest introducing the paper from Jayakar et al., detailing the different diagnostic approaches in candidates for epilepsy surgery, right after the discussion of the benefits of epilepsy surgery (line 49). This details the central role of MRI, EEG, and clinical evaluation, as well as introduces ancillary imaging techniques (i.e., nuclear medicine), which can be extremely valuable, as shown by Lascano et al.

- Discussing the number of patients with positive and negative MRI findings is crucial. Please provide this information.

- The part of the introduction between lines 50 and 69 is a bit chaotic. The ongoing myelination, the discrepancy between EEG and MRI findings, the need for sedation, lesion localization in eloquent brain areas, lesion boundaries definition, MRI negative cases, subtle findings (i.e., small periventricular grey matter heterotopia, or glial scars), are general problems affecting the pediatric population not only patients with malformations of cortical development, FCD or MRI negative cases. Also, magnet field strength massively affects the detection rate.

- The 1.3 Objective paragraph lacks one of the prominent categories of readers: Pediatricians

and Neuropeadiatricians. In the end, the manuscript is submitted to Translational Pediatrics.

**Reply 1**: added the information as suggested, please check page 2, line 36
**Reply 2**: added the references as suggested, please check page 3, lines 67-75.
**Reply 3**: added the information, please check page 2, lines 45-48.
**Reply 4**: edited and formatted the introduction part for a better understanding and readability, please check page 2, lines 41-52.
**Reply 5**: added the information, please check page 3, line 91.

Discussion

- A possible idea would be to prepare a table containing the technical aspects of each sequence and a representative image. This would free the discussion from technical aspects, focusing the discussion on the histology benefitting the most from each sequence.
- Paragraph 3.1: I would briefly introduce the physical background of diffusion imaging rather than the year of its introduction. Since several diffusion techniques have been developed, why not subdivide this paragraph into subparagraphs discussing each approach separately? Also, the results of Lorio et al. (on NODDI) and Gennari et al. (on DTI) should be highlighted, being the sole to provide quantitative discrimination between FCD types.
- Paragraph Double inversion recovery: Which are the "subtle lesions" DIR helps detect?
- Arterial Spin Labelling Paragraph: In my opinion, this paragraph should include the paper from Tortora et al., that of Rutten et al., as well as that of Gennari et al., even though the latter was published in March 2024 because it addresses some of the drawbacks of the use of sedatives. Furthermore, these papers deal with ASL in children with focal drug-resistant epilepsy, providing evidence on specific etiologies. Further, the introduction of multi-delay ASL could be briefly touched.
- Quantitative imaging Paragraph: The paper from Casella et al. should be included.
- Ultra-high Field Paragraph: Please provide quantitative data supporting the signal-to-noise and contrast-to-noise ratio improvements and the increase in detection rate. Also, 7T correlated with ex-vivo specimens (as shown by Zucca I. et al.) showed innovative findings in some pathologies (i.e., a dark band on susceptibility images in FCD
- Paragraph 3.2: While not precisely a postprocessing technique, manual segmentations overlay and the study of Wagstyl et al. should be mentioned. Having an atlas of FCD location represents one of the main advances of the last decades.

1) in the VBM paragraph, why not provide a graphical representation of the image analysis needed in VBM and MAP? As such, they could have detailed the benefits of VBM for specific histology or the differences between SPM and FSL.
2) Please correct the typo (VBN).
3) Please define MAP.

- Surface-based morphometry Paragraph: While the review has discussed focal lesional epilepsy, in this section, BECTS is introduced. This is misleading. BECTS cases do not proceed to surgery, being a self-limiting disease. Hence, it does not fit with the

Figures

- Please refer to the first comment of the discussion.

**Reply 1:** table added at the end of discussion, please check page 15, lines 386-387. We cannot include images because we don't own the copyright for some of the sequences.
**Reply 2:** edited and added the information, please check pages 4-5 lines 117-121 and 132-139.
**Reply 3:** Removed the part about subtle lesions as it is no longer deemed appropriate.
**Reply 4:** added the references as suggested, please check page 7 lines 186-193.
**Reply 5:** added the references as suggested, please check page 8 lines 215-218.
**Reply 6:** added the information, please check page 9 lines 252-255.
**Reply 7:** added the information, please check page 12 lines 361-363.
**Reply 8: u**nfortunately, VBM has not been implemented at our institution, and we cannot include images related to VBM because we do not own the copyright.
**Reply 9:** corrected the typo, thank you.
**Reply 10:** MAP defined, please check page 10 lines 288-290.
**Reply 11:** removed the part about BECTS as it is no longer deemed appropriate.

**Reviewer C**

Well-written review on an important topic
1. Figures - explain the finding (blurring of grey-white junction) to help clarify that why is the lesion a FCD (helpful for junior members and trainee readers)
2. Reference the figures in the text
3. Correct minor typographical errors - line 288, change VBN to VBM
4. The title of the study states "pediatric focal epilepsy" - it would be great if the authors could specify specific pediatric studies related to each neuroimaging modality (the age groups included in these studies) and address the limitation of each of these modalities in children. Also elaborate on other MCDs in children (PMG etc) that may be operable and how these imaging modalities may help or not.

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**Reply 1:** added the information, please check Figure 1 (page 6, lines 162-163), Figure 5 (page 12, lines 366-367).
**Reply 2:** added, please check page 11, line 358.
**Reply 3:** corrected, thank you**.**
**Reply 4:** table added at the end of discussion, please check page 15 lines 386-387. Please consider that we have chosen to report only the starting age of patients included in the study because some studies are new and still being explored. Consequently, the patient cohorts encompass both pediatric and adult patients.

**Reviewer D**

#1. Additional tables are informative to readers to characterize MRI sequences and post-processing techniques, especially their relevance to histopathological diagnosis of FCD types.
#2. ASL is also useful to evaluate status epilepticus, though whole network can be hyperperfusion area instead of restricted seizure focus.
#3. Figures should be indicated woth age and reference literatures.

#4. As for fMRI figure, it is better to superimpose on patient's own MRI because anatomical configuration is different from normalized image.

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**Reply 1:** table added at the end of discussion, please check page 15 lines 386-387
**Reply 2:** Thank you for your comment. However, we have decided not to report ASL in status epilepticus as we focused our attention on focal epilepsies. Additionally, seizure-associated MR changes are a complex and still controversial topic in the literature.
**Reply 3:** added data as suggested, please check: Figure 1 (page 6, line 161); Figure 2 (page 7, line 176); Figure 3 (page 8, line 207); Figure 4 (page 11, line 326) Figure 5 (page 12, line 365).
**Reply 4:** The fMRI areas are superimposed onto the surface images of the patient, not a normalized map. We decided to use a surface map image because it provides a clearer and more detailed view of cortical activations on the brain's surface. The surface map also simplifies the interpretation of fMRI data, particularly for clinicians and researchers who may not have extensive training in neuroimaging.