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First external peer review

Reviewer Comments

COMMENT 1:

The authors report an overview of pediatric epilepsy surgery, including history and perspective. It's a fairly comprehensive overview, but I have a few major concerns

The first concern is that the very specific aspects of surgery for pediatric epilepsy are not emphasized enough, such as: so-called "**catastrophic" epilepsies, infant epilepsies, multifocal epilepsies (including tuberous sclerosis) requiring a specific procedure in the decision to operate and the way to explore -if necessary- with invasive recordings: for example, SEEG is not feasible below 18-24 months and subdural electrodes are the only way to explore if necessary**. Similarly, **surgery in several stages must sometimes be considered (for Hypothalamic hamartoma for example**..) It is also important to emphasize the requirement of a multidisciplinary team dedicated to the care of children only. In general, the authors develop an argument more suited to adults than to children (for example in the chapter "temporal epilepsies" the authors report 44% of temporal surgeries, which corresponds to the rate for adults and not for children (23%). One of the aspects of epilepsy surgery is the need to discuss on a case-by-case basis and to offer tailored surgery rather than standardized surgery. Similarly, most of the references cited concern adult series or mixed series but rarely pure pediatric reports: ex ref 29, 43, 54, 56….

Reply 1: Thank you very much for these comments and points to be addressed. The

points of view brought up have been seriously considered and addressed in the context of our manuscript.

1. We have added more detailed analysis of specific epilepsies as mentioned.
2. We did discuss staged surgery in our original version, but note the reviewers comment, and have expanded on this topic.
3. We also describe the importance of multidisciplinary care for this cohort as a critical element as well as the importance of case-by-case analysis of children who meet criteria for medically refractory epilepsy.
4. With regards to, the discussion of adult versus children epilepsy surgery, we understand the mention of reports including adult and children, a good majority of the literature is inclusive of both adult and children cases. Therefore, to exclude this from our manuscript, we felt would be a major shortcoming and would be a severe limitation to the paper. The mention of temporal surgeries

Changes in the text:

Various changes have been made given the broad reaches of the reviewer comments. Changes have been highlighted between pages 8-17 and lines 163- 412.

COMMENT 2:

The second important remark concerns the chapter " disconnective surgery" which has some omissions:

L 137: "….Various techniques have been described with an endoscopically-assisted hemispherectomy approach being most recently described….. (25)"

Prior to endoscopically assisted hemispherectomy, new surgical procedures were developed that reduce the volume of brain removal and increase the ratio of disconnection to resection. These surgical techniques require a smaller skin incision and bone flap, which offers the advantages of reducing blood loss and avoiding the exposure of large venous sinuses. This concept replaces the term "hemispherectomy" with "hemispherotomy," as proposed by Olivier Delalande in 1992 .ref: Delalande O,

Pinard JM, Basdevant C, Gauthe M, Plouin P, Dulac O: Hemispherotomy: A new procedure for central disconnection. Epilepsia 33 [Suppl 3]:99–100, 1992; Delalande O 2004. Parasagittal hemispherotomy) which is widely performed must be mentioned. Likewise endoscopic trans ventricular disconnective surgery (Delalande 2003) which was performed before the development of LITT for Hypothalamic hamartoma (and remains nowadays an option) must be mentioned as well as the disconnection associated with focal resections in large frontal or posterior epilepsies usually due to large cortical dysplasias.

Reply 2: Thank you for this comment. We have included this mention in the hemispherectomy section.

Changes in the text: Changes to hemispherectomy section page 19 lines 455-467 include the mention of alternative disconnection surgical approaches.

COMMENT 3:

The third important remark concerns the history of invasive explorations with contains imprecision and anachronism:

L 118: "…… in the 1930s, Penfield and the Montreal Neurological Institute were the first to utilize invasive electrodes for long-term EEG monitoring, which paved the future way for the technique we term stereoelectroencephalography (SEEG)…..

The term SEEG was first mentionned In the 60s by Talairach et al following the use of depth electrodes set using a framework. , (Bancaud J, Talairach J, Bonis A, Schaub C, Szikla G, Morel P, et al. La stéréoélectroencéphalographie dans l'épilepsie. Paris: Masson; 1965. Talairach J, Bancaud J, Szikla G, Bonis A, Geier S, Védrenne C. Approche nouvelle de la neurochirurgie de l'épilepsie. Méthodologie stéréotaxique et résultats thérapeutiques. Neurochirurgie 1974;20:1–249.

The electrodes were inserted without any bone flap. This method allowed a tridimensional study of the interictal activity and the seizures, including the onset and the propagations as well, making correlations with clinical ictal features possible. First described as acute, the development of well-tolerated electrodes gave birth to

chronic recording. Subdural electrodes were used in North America and by physicians in other countries having been taught in the U.S.A. and Canada whereas SEEG was developed in France and Italy. In recent years, SEEG has been 'rediscovered' in Cleveland and has led to widespread use around the whole world. Ref: Gonzalez-Martinez J, Bulacio J, Alexopoulos A, Jehi L, Bingaman W, Najm I. (1): early experience from a North American epilepsy center. Epilepsia 2013;54:323–30.

REPLY 3: We thank you for the contribution and critical point of view. We have adjusted our mention of the history of SEEG by including the references of Tailarach and company, as well as giving much credit to the Cleveland group on their broadening of the utilization of SEEG.

Changes in the text: We added the necessary features in Page 6-7,Lines 139-144

COMMENT 4:

L 123: “In 1938, McKenzie utilized SEEG first for hemispherectomy…”

The use of the term SEEG in this sentence is anachronistic because SEEG has not yet been designed. Please specify the exact method used (probably Ecog)

The third remark concerns chronic invasive recordings (SEEG and subdural electrodes) which need to be further developed. This includes their use, choice of method, role in identifying the epileptic zone, electrical stimulation to elicit the eloquent cortex as well as therapeutic implication such as SEEG-guided radiofrequency thermocoagulations

REPLY 4: Regarding McKenzie, much apologies. SEEG was not utilized here, rather, he is credited with performing the first hemispherectomy in 1938.

Changes in the text: We edited page 7, line 145

COMMENT 4:

Minor remarks.

L 206: "….Transcranial magnetic stimulation is an option for the functional mapping of key eloquent regions before surgery to create a safer pathway for surgical resection……."

Please also mention the key role of cortical stimulation in identifying the eloquent cortex during chronic (subdural or SEEG) recording achievable from 2 years of age

REPLY 4:

Thank you for this comment. We have provided an additional reference regarding this in the preceding text.

Changes in the text: We have added this to Page 11, line 249-250.

COMMENT 4:

L 234: "…In non-lesional epilepsy, invasive surgical encephalography may be discussed."

Invasive EEGs may also be required in some lesional epilepsies.

REPLY 4: Thank you. We have provided that open-ended change in the text.

Changes in the text: We have added text to lines 279-280 on Page 12.

COMMENT 5:

L244: "…The risks of a multi-stage operation include CSF fistula, meningitis, wound infections, scar formation, neurological deficit, edema, and withdrawal from antiepileptic medications. As an alternative, Bansal et al. described the prospective study of single stage surgical resection with intraoperative electrocorticography…"

Such a list of undesirable effects must be nuanced according to the methods of exploration. SEEG, even in young children, is safe and well tolerated, provided that a

minimum period of one month is observed between exploration and resection, whereas invasive explorations with subdural electrodes indeed carry a higher risk of wound infection and meningitis (Taussig 2020).

REPLY 5: We appreciate this comment as our initial text seemed a bit unclear. It is more appropriate to further identify the differences in SEEG and subdural grid placement with respect to risk profile. The changes have been made and the reference by Taussig has been included in the text.
Changes in the text: We have made the necessary additions to page 12-13, lines 288-309.

COMMENT 6:
L 275: "…Anteromesial temporal lobectomy makes up 44% of resective surgery in children…"
Please cite reference for this rate of 44% which appears high for children population. In the paper written by Harvey S (epilepsia 2008) the rate for temporal surgery in children is 23.2%.

REPLY 6: The rate was 41% as reported by Harvey in 2008, but that was to include frontal and temporal, with a subcategory of 23.2% in temporal lobectomy. Thank you for noticing this error, and we have correctly modified this in the text, and further characterized, that since the 2008 report by Harvey in 2015, another article describes the US reports of volume, with temporal lobectomy being performed at lower absolute rates.
Changes in the text: We have made the respective changes to Page 14, lines 337-347

COMMENT 7:
L 300: "…They showed classic MTS had the best outcomes, with atypical mesial sclerosis demonstrating less benefit.
In childhood population mesial sclerosis is not the main etiology (15% versus 44% in adults) see Blumcke I 2017

REPLY 7. This comment does not state that MTS is the main etiology of epilepsy in children, it just states the success of the surgery as demonstrated by York et al. We recapitulate that focal cortical dysplasia is the most common etiology of childhood epilepsy and is not seen in the temporal lobe as much as it is in extratemporal regions, such as the frontal lobe.

Changes in the text: We have added text to page 15-16, lines 376-400

COMMENT 8:

L 303 "extratemporal epilepsies…"

This chapter should be further developed because it is the most frequent situation in children, including multilobar epilepsies and multifocal epilepsies such as TSC.

REPLY 8: Thank you for this, and we believe we have spent the required due diligence to expand this section as it deserves much needed attention.

Changes in the text: We have expanded this section Pages 16-17, lines 391-412.

Second external peer review

Reviewer A

This manuscript tries to squeeze the history and practice of pediatric epilepsy surgery into a journal-style article, and fails to do so. In my opinion, to be justified for publication a narrative review must excel in several areas (to account for the relaxed requirements regarding scientific rigour etc). It must be excessively well written and allow the reader to gain a workable knowledge in a given field. This manuscript does neither. It is very inconvenient to read. The reader is left alone with a plethora of percentages which only seem to be comparable, in fact the outcomes of the different surgical procedures are always, and foremost, dependent on the identification of the

right patient for the right surgical approach. Furthermore, the one really new and important aspect in epilepsy surgery, the role of epilepsy surgery in the context of proven or suspected genetic disorders, in entirely ignored.

Reply 1: Thank you for the commentary, as well as the critical analysis of the paper. We hope to have properly revised the manuscript to improve its readership and overall quality.
Changes in the text: N/A

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* Abstract

- "impacted by patients with DRE": this phrase seems to imply that the patients are cause, and not victims, of the loss of QoL; I am, however, not a native speaker and might be wrong

- "surgery for DRE has been conducted since the late 1990s" - in children? 1990s seems to be too late

- Methods: I don't see any reason to list all the sections, but this is a stylistic remark

- "simulation-based techniques" - sTimulation

- "The dearth of literature on this topic should be highly considered for all practitioners who manage children with epilepsy" - what does this mean?

Reply 2: We thank the reviewers for their comments. We have revised the abstract to improve readership and clarity.
Changes in the text: Changes have been made between lines 45-59

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* Introduction

- "Of the 50 million people described worldwide, 1/3rd of patients with epilepsy are inadequately controlled with medications." - who are the 50 million? What does "1/3rd" mean?

- "with up to 40,000 diagnosed with epilepsy by age 18." - 40000 in which group? The US, the world?

- "Of those who develop epilepsy, up to 30% will become refractory to multiple antiepileptic agents." This is a reptition of the statement with the "one third"

- "Patients who don’t respond to first-line agents are less likely to respond to second line agents" - well, patients that respond to first line agents usually don't even need the second line agents

- "Pediatric DRE is more complex when compared to adults with DRE." - what does "complex" mean in this context?

- "undertreated epilepsy may have longstanding consequences, for which early identification of DRE may be critical." - for the "untreated" epilepsy, any kind of treatment would be beneficial, "untreated" is not the same as "drug resistant" or "insufficiently treated" - "In 2008, over 70% of surgical cases were readily apparent operative epilepsy cases." - this seems to be a rather blunt switch of the topic to epilepsy surgery

- This section needs a complete overhaul, it is very inconvenient to read and does not have a structure that guides the reader

Reply: Thank you for the comments. We have clarified several statements are listed above and reorganized the introduction for improved readership.

Changes in the text: Changes have been made between pages 3-4, lines 131 to 215.

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* Methods

- "standard search engines" - there are no "standard search engines"

- Table 1: Please provide, as requested, at least some examples for the actual search strategy. Searching for "pediatrics" alone yields 1,115,873 results, I guess that some kind of AND / OR

combination has been used

- "(Available at https://tp.amegroups.com/pages/view/guidelines-for-authors#content-2-2-2)"

I don't think that the reader needs to know where to look for the checklist

- "Individuals such as Dr. Macewen and Dr. Harvey Cushing helped spearhead the creation of the ILAE in the early 20th century."

- maybe, but where is the connection to the topic of this manuscript?

- "While" - "while" - I don't think that the use of this word is justified in all the instances it occurs in this section

- I personally think that the mentioning of all the names should be sarcificed and replaced by a structure that follows the topics rather than the names

- "with strong evidence for temporal and extratemporal epilepsy lacking in children. "

- what does this mean?

- "nearly half believed the failure of two antiepileptic agents defined drug-resistant epilepsy." - but they are right, aren't they? Furthermore, the word "believe" seems to be misplaced here

- "Englot et al and the ILAE encourages the need for referral of medically refractory pediatric patients to comprehensive epilepsy centers, assuming that all comprehensive epilepsy centers, have multidisciplinary care, including neuropsychological and neurodevelopmental testing." - Repetition of the above

- "are appropriate diagnoses for surgical referral." - surgical or pre-surgical?

- "Advancements in neurological imaging for epilepsy may not be available for some patients" - what does this mean? Is this a statement regarding the availability of modern methods in countries with a less developed health system?

- "for identifying hypometabolic regions associated with seizure events" - this is not correct. PET shows a hypometabolism, but in the interictal phase, therefore seizures must be ruled out during the PEC. SPECT shows ictal hyperperfusion, and

magnetoencephalography is something entirely different

- "high-definition MRI, ictal SPECT, and/or invasive SEEG" - I would require a high-definition MRI in any case of epilepsy surgery. SPECT not necessarily, SEEG in most cases

- "Transcranial magnetic stimulation is an option for the functional mapping of key eloquent regions before surgery to create a safer pathway for surgical resection and has been described to have efficacy in cortical epilepsy not amenable to resection." - this mixes the different uses of TMS

- "is seen in cryptogenic or catastrophic epilepsies," - these are two entirely different categories. "catastrophic" is, futhermore, not the recommended nomenclature

- "There are over 120,000 children hospitalized with epilepsy alone, compared to 2,000 who obtain pediatric surgery per year." - worldwide?

- "The first cases of pediatric epilepsy set the precedent for treating a life-altering, debilitating condition," - what does this mean?

- "As can be applied in lesional epilepsy," - misplaced after the last phrase listed the different forms of epilepsy suergery.

- "requires, a two-stage" - a comma to much

- "but cannot be performed until approximately three years" - I think that there are cases where this is not correct

- "In their cohort, rates o80% seizure freedom Engel class I were seen, there were no major neurological complications and 3% had minor or temporary complications." - this implies that single stage surgery with intraoperative elektrocoricography is somehow superior. This is not the case. This was certainly a cohort with a very clear epileptogenic lesion, which of course improves outcome

- "Younger children may have multifocal pathology, in the presence of solitary lesions, making ancillary testing necessary, in comparison to older children and adults. " - please support with data

- "In pathologies such as Sturge-Weber" - of course, in this case you know the

epileptogenic region even before doing the first EEG.

- "65% achieved Engel class I." - please explain as not all readers are familiar with the Engel classification
- Line 357: A comma seems to be missing
- "Focal cortical dysplasia may be discrete but commonly requires wide resection margins." - this does apply to temporal lesions, too
- Line 370: "compared to brain tumors" - this is true for LEAT, other brain tumors are frequently extratemporal
- "Selective amygdalohippocampectomy" - this section might better be placed to the temporal surgery methods
- "with subsequent magnetic resonance technology to detect thermal applications to the target" - what does this mean?
- "A multicenter analysis described the evolution of the Hemispherectomy Outcome Prediction Scale evaluating outcomes of over 1200 patients." - this phrase seems a little bit lost here
- "The feared complication in this surgery is disconnection syndrome" - being what?

Reply: Thank you for this commentary. We did our best to respect each and every bullet point provided by the reviewer and made edits to the text as needed. We do feel that the mentioning of key historical pioneers in pediatric epilepsy surgery is integral to the message we aimed to portray. We believe that it conveys an important image to the reader that a variety of figures throughout the world had a role in innovation in this surgical arena.

Changes in the text: A variety of changes have been make to the discussion section, from page 5 until 21 from lines 250 to 860.

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* Conclusions

- I can't see why these conclusions are justified or supported by the text before

Reply: Thank you for this comment. We have made changes to the conclusion

Changes in the text: Lines 912 to 919.

Reviewer B

This is a well written narrative review. While the subject matter may be more of an interest for clinicians or health allies involved in pediatric epilepsy and epilepsy surgery care, nonetheless, it should be sufficiently appealing for general readers outside of the neurosurgery/neurology specialty. The review can also be used as an education material for students, researchers, neuroscientists, EEG scientists working in the related fields. The review is well formatted, met all the requirement by the journal. While I have no major concern about the content of this work, I have a few suggestions that I like the author to incorporate. I think incorporating these changes will improve the over content and experience of reading this work:

Reply 1: We appreciate the commentary. Given additional reviewer commentary, we have worked diligently to improve the review even more to enhance its quality furthermore.

Changes in the text:

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1. I would like to see the work to include figures showing:

i) example MR images of pediatric epilepsy pathology (e.g. FCD, TSC, developmental brain tumour such as DNET, GG..etc, cavernoma, HH..etc) demonstrating a range of different pathology in both temporal and extratemporal

locations;

ii) either clinical case examples or illustrations showing the different surgical approaches and/or techniques, to accompany the main text descriptions. I believe they will help general readers without a neurosurgery background to better understand and appreciate the content of this work.

Reply 1: Thank you for the comment. We appreciate this point of view, although taking generic pictures of brain tumors for patients with clinical context or a proper thorough decision making tree would convolute the paper a bit more. We hope to have provided an overall context of these illnesses, and as providers are aware of the diagnoses of the patients they can search for the images themselves.

Changes in the text: n/a

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2. The author had touched on the increasing role of advanced neuroimaging in the surgical care pathways for these children, which I agreed. However, I would like the author to expand on this a bit more, by also mentioning the role of BOLD fMRI and the use of diffusion MRI tractography in presurgical planning and intraoperative image-guidance (neuronavigation)- as surgical adjuncts to map key eloquent regions, and the associated white matter tracts. This is particularly relevant when operating in or adjacent to eloquent brain areas, to avoid surgical injuries and for postoperative functional preservation. Please consider citing the following works:

-Yang JYM, et al, Frontiers in neuroscience, 2019, Optic Radiation Tractography in Pediatric Brain Surgery Applications: A Reliability and Agreement Assessment of the Tractography Method; https://www.frontiersin.org/articles/10.3389/fnins.2019.01254/full

-Leon-Rojas J, et al, BJR Open, 2021. (1); https://www.birpublications.org/doi/full/10.1259/bjro.20200002

-Yang JYM, et al, Phys Med Bio, 2021, https://pubmed.ncbi.nlm.nih.gov/34157706/

-Yang JYM, et al, JNSPeds, 2017. A systematic evaluation of intraoperative white matter tract shift in pediatric epilepsy surgery using high-field MRI and probabilistic high angular resolution diffusion imaging tractography; (2)

Reply 2: Thank you for this point. We have added this context in the manuscript.

Changes in the text: We have made these additions and changes line 561 to 564.

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3. Please briefly comment on the role of intraoperative MRI in pediatric epilepsy surgery (that improves GTR rates, GTR being an important determinant of postoperative seizure outcomes) . Please consider citing this systematic review:

Englman C, et al. J Clinical Neuroscience, 2021. Intraoperative magnetic resonance imaging in epilepsy surgery: A systematic review and meta-analysis; https://pubmed.ncbi.nlm.nih.gov/34373012/

Reply 3: : Thank you for this recommendation. We have added this reference and associated text to the manuscript

Changes in the text: We have made these additions and changes line 564 to 566.

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4. The authors have stated identifying epileptogenic focus in cases with multifocal

epilepsy (such as multiple tubers) being a challenging clinical scenario. I think the opposite scenario deserves a mention, too. Identifying subtle focal cortical dysplasia (especially ones confined to the bottom-of-sulcus, BOSD) are also very challenging. The ability to identify and resect BOSD can have transformative impact on the seizure and neurocognitive outcomes in these children. Advances in neuroimaging techniques, including high resolution structural images from clinical high-field 3T systems, and in combination with metabolic imaging such as PET, ictal SPECT or SPECT-SISCOM images, also played critical roles in detecting these subtle FCD lesions. Please cite this study by Harvey A.Simon et al, neurology, 2015; https://n.neurology.org/content/84/20/2021.short

Reply 4: Thank you. We have added the reference and provided some greater insight into the clinical scenario.
Changes in the text: Page 12 lines 527 to 530.

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5. Page 9, surgical approach section, describing single staged intraoperative electrocorticography-guided resection as an alternative to 2-stage surgery with invasive intracranial monitoring. Please also mention and cite this BOSD surgical series by Macdonald-laurs E, et al, as another good example showing good seizure outcomes with the one-stage approach and also utilising advanced multimodal imaging techniques (namely language BOLD fMRi and tractography) to aid presurgical planning, and to achieve postoperative functional preservation. [Macdonald-Laurs E, et al, Neurology, 2021. One-Stage, Limited-Resection Epilepsy Surgery for Bottom-of-Sulcus Dysplasia
https://n.neurology.org/content/97/2/e178.abstract]

Reply 5: Thank you. We have added the reference and provided some greater insight into the clinical scenario.

Changes in the text: Page 12 lines 527 to 530. As well as lines 539 to 558.

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6. The mention of "machine-based learning models' surgical precision…in the conclusion (page 19, line 561) caught me by surprise a bit. I am unsure what the author was referring to. My first reaction was thinking of the use of unsupervised deep-learning algorithm detecting FCD. Andrea Bernasconi's lab from MNI is leading the field on this work. If this was what the author was referring to, then, I think this deserves a mention in a form of a brief paragraph. The author could consider citing the works from Dr Bernasconi's lab, such as these ones:

https://n.neurology.org/content/97/16/e1571

https://ieeexplore.ieee.org/document/4541326

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7520429/

Reply 6:We have removed this from the conclusion as it out of context from the paper and is not discussed in the manuscript.

Changes in the text: Page 23 lines 912 to 919.

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7. Minor: page 12, line 348: MTS should be spelled out in full first (i.e. "Mesial Temporal Sclerosis")

Reply 7: Thank you.

Changes in the text: Page 13 lines 572

Reference

1. Leon-Rojas J, Cornell I, Rojas-Garcia A, D'Arco F, Panovska-Griffiths J, Cross H, et al. The role of preoperative diffusion tensor imaging in predicting and improving functional outcome in pediatric patients undergoing epilepsy surgery: a systematic review. BJR Open. 2021;3(1):20200002.

2. Yang JY, Beare R, Seal ML, Harvey AS, Anderson VA, Maixner WJ. A systematic evaluation of intraoperative white matter tract shift in pediatric epilepsy

surgery using high-field MRI and probabilistic high angular resolution diffusion imaging tractography. J Neurosurg Pediatr. 2017;19(5):592-605.