UPDATE

Expedited epilepsy surgery prior to drug resistance in children: a frontier worth crossing?

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Abstract

Epilepsy surgery is an established safe and effective treatment for selected candidates with drug-resistant epilepsy. In this opinion piece, we outline the clinical and experimental evidence for selectively considering epilepsy surgery prior to drug resistance. Our rationale for expedited surgery is based on the observations that, 1) a high proportion of patients with lesional epilepsies (e.g. focal cortical dysplasia, epilepsy associated tumours) will progress to drug-resistance, 2) surgical treatment of these lesions, especially in non-eloquent areas of brain, is safe, and 3) earlier surgery may be associated with better seizure outcomes. Potential benefits beyond seizure reduction or elimination include less exposure to anti-seizure medications (ASM), which may lead to improved developmental trajectories in children and optimize long-term neurocognitive outcomes and quality of life. Further, there exists emerging experimental evidence that brain network dysfunction exists at the onset of epilepsy, where continuing dysfunctional activity could exacerbate network perturbations. This in turn could lead to expanded seizure foci and contribution to the comorbidities associated with epilepsy. Taken together, we rationalize that epilepsy surgery, in carefully selected cases, may be considered prior to drug resistance. Lastly, we outline the path forward, including the challenges associated with developing the evidence base and implementing this paradigm into clinical care.

Introduction

Epilepsy is one of the most common neurological disorders in the world[1] and has among the highest morbidity of all paediatric diseases. Epilepsy surgery can be a *definitive* treatment for seizures in selected children with epilepsy and has the potential to enable discontinuation of anti-seizure medications (ASMs), maximizing quality of life. In experienced comprehensive epilepsy surgery centres where careful multidisciplinary evaluation is available, epilepsy surgery is both effective and safe.[2] Although the impacts of epilepsy surgery on cognitive and behavioural outcomes are modest, unpredictable, and difficult to quantify, there are data to suggest that surgery improves developmental outcomes, and that longer duration of epilepsy negatively impacts outcomes across multiple domains.[3-5]

Candidacy for epilepsy surgery has traditionally required an identifiable epileptogenic region (with characteristic electrical-clinical-radiological concordance) and drug resistance (DRE) – defined as the failure to control seizures on two adequately trialed ASMs.[6,7] Establishing DRE is often protracted, prolonging the time that affected patients live with seizures, negatively impacting their quality of life. When considered alongside evidence that longer duration of epilepsy negatively impacts post-operative seizure freedom, there has been increased consideration of early surgery.[8,9] While many have advocated for the benefit early epilepsy surgery,[10,11] to our knowledge, no study has evaluated the efficacy of surgical resection *prior* to patients reaching the definition of DRE.

In this *Update*, we explore the clinical, experimental, and theoretical evidence for 'expedited surgery' which we define as evaluation for epilepsy surgery prior to or in parallel with the establishment of drug resistance (Figure 1). We hypothesize that expedited surgery in carefully selected children may reduce the total number of lifetime seizures and advocate that this novel paradigm may be appropriate for experienced comprehensive epilepsy centres. The impacts on long-term cognitive and behavioural morbidity and mortality remain extremely important open research questions. We also explore the barriers to implementing this paradigm into routine clinical care and the challenges associated with developing a robust evidence base to support its widespread adoption.

Lesional epilepsy is often drug-resistant

Identification of a lesion on neuroimaging has been consistently shown to be the most significant factor associated with drug-resistance.[12] Natural history studies have demonstrated that 80-90% of patients with visible focal cortical dysplasia (FCDs) and long-term epilepsy-associated tumours (LEATs) will become drug resistant.[13,14] Surgery for these lesions is effective (i.e. high rates of seizure freedom).[15] Although the evidence for this is not consistent, improvements in cognitive and developmental outcomes can be observed, although these are usually small and may take many years to be detected.[4,6,16]

Epileptogenic lesion resection in non-eloquent brain regions is safe and complications are typically rare and minor (i.e. wound infection, psuedomeningocele, etc.).[13,14] Lesional resection in eloquent regions may harbour risk for deficits in language/speech, cognition, and/or vision (both expected or unexpected),[13,14] but advances in structural and functional neuroimaging as well as pre- and intra-operative mapping continue to markedly reduce these complications. Even in children under 3 years of age, complication rates of lesion resection are exceedingly low in experienced centers.[17]

Despite the evidence of high rates of DRE and the safety and efficacy of surgical treatment, multiple ASMs are often trialed prior to referral for presurgical evaluation, and the associated delays can take years. For example, the median duration of epilepsy prior to surgical evaluation in a recent multicentre study of FCD was 10 years.[16]

Expediting surgery may improve outcomes and reduce time on ASMs

Recent large-scale multi-centre cohort[6] and meta-analysis[18] studies have demonstrated a negative correlation between duration of epilepsy and likelihood of seizure freedom following surgery for patients with FCD. From this, we can postulate that decreasing the duration of epilepsy further prior to the point of DRE may further reduce long-term seizure burden. Reducing the overall seizure burden may also reduce the risk of injuries from seizures and the risk of Sudden Death in Epilepsy (SUDEP).[19] Location of FCD is also associated with seizure freedom; ~75% of patients with lesions in the superior temporal and frontal gyri achieved seizure freedom compared to ~30% of patients with lesions in the visual, motor, and premotor areas.[20]

Extent of lesion resection is associated with rate of seizure freedom,[21] and residual lesion in eloquent areas may explain the lower rates of post-operative seizure freedom in these patients.[20]

An additional consideration for epilepsy surgery prior to drug-resistance is the safety of remaining on high-dose or multiple ASMs.[22-24] Specifically, ASMs may cause late idiosyncratic effects[25] and may have cognitive side effects in children.[26] In addition, there is some evidence to suggest that 1) early-failure of ASMs portends inevitable ASM failure, and 2) the quicker ASMs can be withdrawn, the greater the improvement in intelligence measures.[27,28] Therefore, ASM use in a 'surgically treatable' and potentially curable disease such as lesional epilepsy should be challenged. Finally, since many children can safely discontinue their ASMs after surgery and are more likely wean off ASMs,[6] earlier withdrawal may improve the safety of epilepsy treatment overall.

There may be additional benefits of expedited surgery beyond reduction in seizure frequency

Whilst the International League Against Epilepsy (ILAE) and Engel outcome classifications reliably measure the efficacy of epilepsy surgery using seizure frequency,[29] there are other outcomes to consider after epilepsy surgery. Although some positive outcomes in language, memory, intellectual, and behavioural development[4,5,30-32] have been identified, the magnitude of these effects are usually small, variable and extremely unpredictable. For example, children who receive epilepsy surgery are more likely to improve their intelligent quotient (IQ) score compared to patients treated with pharmacotherapy alone (39% vs 10%), an effect that is more obvious after drug reduction.[5] There is also an association of decreased attention-deficit hyperactivity disorder (ADHD) symptoms after epilepsy surgery.[31] Specifically, children with higher baseline scores on the Conners 10-item scale and those who received right-sided surgery were most likely to see reduction in symptoms; however, the magnitude of change is small (~2 point reduction on the Conners 10-item scale).[31] Finally, observational studies of parent/carer reported outcomes suggests improvements in emotional and behavioural measures after epilepsy surgery, although follow-up time is limited (< 2 years) and standardized measures across studies are needed.[30] All of these studies are 'end stage' and there remains an open hypothesis that early intervention will limit the extent of cognitive impairment, given the relationship between cognition and epilepsy duration. However, the length of time typically required to see

measurable improvement in one or more cognitive domains is substantial (often > 2 years). Large-scale, prospective studies are needed to systematically evaluate neurocognitive effects of epilepsy from the point of diagnosis and firmly establish whether surgery (and stopping seizures) has a significant impact on developmental trajectories.

An additional benefit of expedited surgery is expedited histopathological diagnosis.[33] Reaching a histopathologic diagnosis may have clinical relevance (i.e., differentiation between LEAT – and LEAT subtype – and FCD type) for prognosis, surveillance and treatment. For instance, integrated histopathological, molecular and genetic diagnosis may pave the way for targeted therapies in patients not rendered seizure free following surgery.[34-36, 37,38]

Expedited surgery may limit brain network dysfunction

Focal epilepsy is an archetypal brain network disease. Brains harbouring FCD display volumetric (structural covariance), structural (diffusion MRI) and functional (functional MRI) network abnormalities that extend beyond the boundaries of the lesion.[39-41] Indeed, network abnormalities are likely present at disease onset and may be useful biomarkers of drug resistance.[42] One hypothesis of drug-resistance for FCDs is that repeated seizures or abnormal electrophysiological activity in the absence of seizures modulate synaptic weightings of brain networks beyond the epileptogenic lesion thereby negatively impacting function.[43] There are some data to support this concept derived from a kainite model of temporal lobe epilepsy in mice, where persistent interictal epileptiform activity is observed despite removal of the focus, although it is difficult to control for the extent of damage from kainite alone.[44] Early focal resection might improve global neurocognitive function by limiting progression of maladaptive neural connections.[5] There is evidence that alterations in white-matter tracts and network topology (measured by quantitative anisotropy) progress over time in patients with temporal lobe epilepsy and that greater reduction in aberrant connections after surgery leads to improved seizure outcomes in patients undergoing anterior temporal lobectomy.[45] We hypothesize that surgical intervention prior to drug-resistance will attenuate development of maladaptive neural networks, improving seizure freedom and neurodevelopmental outcomes.

'Big data' combining neuroimaging, genetics, and histopathology information are advancing our understanding of global brain structural and functional alterations in epilepsy.[46]

Large-scale neuroimaging studies have demonstrated that focal epilepsy is associated with dysfunction of brain networks and brain-region specific volume changes correlate with longer duration of disease.[46,47] Age at diagnosis, age at surgery, and histopathology (LEAT, hippocampal sclerosis, and vascular malformation) are the most important factors predicting seizure freedom after focal epilepsy surgery.[6] Furthermore, both MRI-positive and -negative epileptogenic foci display similar genetic and pathologic findings, which are highly correlated with drug resistance.[6] Approaches to more rapidly and precisely identify epileptogenic lesions will facilitate earlier surgical intervention.

Expedited surgery may be cost effective

Epilepsy surgery is highly cost-effective and shifting to expedited surgery in a cohort of patients that are highly likely to become drug resistant in the long term may make it an even more cost-effective intervention by saving on ASM management, hospital admissions and routine clinic visits.[48,49] This is perhaps even more of a consideration in low and middle income countries (LMICs), where there are identified disparities in access to epilepsy care and epilepsy surgery and increasing such access could lead to both direct and indirect cost gains.[1,50] With ~80% of global epilepsy burden in LMICs, initiating surgical programs for lesional epilepsy may help alleviate disease prevalence given the paucity and challenges of, safely managing ASMs.[51] Development of epilepsy surgery programs in LMICs is possible,[52,53] and expedited surgery may play an even larger role and have a larger impact in these settings.

There may be barriers to the paradigm of expedited epilepsy surgery

Despite the lack of robust evidence in certain areas, we have synthesized a biological, clinical, and economic rationale to consider expedited epilepsy surgery for FCDs and LEATs. The adoption of an expedited surgery paradigm has several challenges, many of which are inherent to epilepsy surgery, but are exacerbated by the novel accelerated timeframe.

First, there remain significant barriers to referring clinicians and patients/carers considering surgery for the treatment of epilepsy. Despite decades of reported experience and increasing physician and patient/carer education, misconceptions persist about the relative safety

and comparative efficacy of surgery and long-term ASM exposure. Further, widespread global inadequate access to comprehensive epilepsy centres and socioeconomic barriers impede early referral and the potential opportunity to undergo surgery.[9,54] To offer expedited epilepsy surgery in children with lesional epilepsy requires a carefully considered and informed discussion between an interdisciplinary provider team, the caregivers, and the patient. We envision an early clinic visit where treatment options are discussed including expedited surgery, early presurgical evaluation with continued trial of medication alone, and the current paradigm of awaiting the development of drug resistance prior to surgical evaluation. The risks and benefits of surgical intervention (potential to stop seizures, cease/reduce ASM use, and surgical complications) and long-term ASM use (toxicities, life-long use) should be discussed using the best available data-driven recommendations. Careful consideration of the individual patient's neuroimaging findings, neurocognitive function, comorbidities, current ASM regimen, and complication rates should inform these discussions. These challenges are evident in both resource-rich and -poor settings.

Secondly, there remain significant delays in pre-surgical evaluation, specifically EEG videotelemetry services, which require specialist infrastructure and expertise.[55] However, in our view, which we acknowledge is not uniformly agreed,[56] ictal EEG may not play a significant role in presurgical decision-making in patients with unilateral epileptogenic MRI abnormalities. In this particular subset of patients who have well controlled epilepsy, ictal EEG may also be difficult to obtain and drug reduction to elicit seizures may be associated with risks (e.g. status epilepticus and injuries) that require careful weighing against the potential benefits. An interictal EEG may be sufficient in these circumstances to rule out generalized epileptiform activity and may reveal topographically concordant interictal epileptiform activity.[57-60] Early referral to comprehensive epilepsy centres that have made a concerted effort to streamline the presurgical evaluation process would undoubtedly help mitigate this issue and may even facilitate even earlier assessment of more complex cases, such as lesion negative children by freeing up videotelemetry services. Although 30% of FCDs may be 'MRI negative',[20] increasing the identification of these lesions through quantitative analyses of MRI scans may aid prompt radiological diagnoses and facilitate expedited surgery even in these more complex cases.[61,62]

Given recent advances in low-cost, portable MRI machines,[63] it is not unreasonable to imagine that such changes in presurgical evaluation paradigms may also aid the establishment of

robust epilepsy surgery programs in LMICs, with associated benefits both at individual patient and health economic levels.

Whilst the idea of expedited epilepsy surgery has the potential to improve outcomes in children, it should only be considered in the hands of highly experienced comprehensive epilepsy centres. As such, these approaches may be prone to experimental bias as well financial conflicts of interest. Thus, consideration of candidacy evaluation and implicit bias generated from the practice patterns and healthcare climate at an individual institution must be carefully considered when implementing epilepsy surgery prior to established DRE.

There are also challenges to developing the evidence base

A final challenge is developing the evidence base to demonstrate the efficacy of expedited surgery. Here, we outline potential avenues for study that would establish the evidence base, acknowledging the many challenges associated with running such studies.

Whilst randomized controlled trials are the pinnacle of the medical evidence hierarchy, patient/public involvement work is needed to identify if such a study – i.e., randomization patients to expedited surgery or standard care arms – would be acceptable and feasible. An essential prerequisite would be to establish whether referring clinicians would refer their patients into such a study. Thus, equipoise[64] in the paediatric epilepsy community is required to shape the future of expedited surgery. Some may argue that waiting for drug resistance minimizes the number of children undergoing surgery and may improve localization if ictal EEG videotelemetry is obtained for every child. However, given the proliferation of literature and endorsement of epilepsy surgery through international governing bodies such as the ILAE (going back over 15 years),[65] it is not unreasonable to think that a paradigm shift of considering expedited surgery in selected lesional epilepsies could occur.

Another major challenge is in assessing the correct outcomes (time to first seizure, seizure freedom, neurocognitive outcomes, etc.) at appropriate timepoints. In addition to seizure frequency, cognitive and quality of life outcomes measures are equally important.[66] Cognitive benefits of surgery may not be quantifiable until late time points post-operatively.[5] Thus, age-specific metrics (adjusted over time) are essential for accurately measuring the efficacy of surgery. Expedited surgery necessitates challenging traditional paradigms of measuring

outcomes at a fixed time from surgery, otherwise there would be mismatch in randomization arms (Figure 2). Rather, we propose using time from randomization (i.e., time of FCD/LEAT diagnosis on MRI) as 'time' in a time-to-event analysis. This is because those in the early surgery arm are more likely to experience recurrence whilst more patients in the standard care arm are likely to have undergone surgery. Therefore, use of a fixed time-point would not accurately facilitate comparison and result in mismatched cohorts (Figure 2).

However, we acknowledge that robustly establishing the benefits requires long-term follow-up of neuropsychological and developmental outcomes. The effect size may be small, requiring a large sample size, will be confounded by heterogeneous baselines and such studies may prove very expensive and onerous to run. In addition, select experienced centres that are already offering such expedited surgery may see it as unethical to randomise patients to surgical treatment at drug resistance. Ultimately, large prospective registries during the paradigm shift (i.e. when there is variation in treatment across centres) may be an alternative means to generate the required evidence base.

Population-level risks-benefit balance may be optimised by improving our ability to predict drug resistance at disease onset.[42,67] Comprehensive deep phenotyping and multimodal assessments including MRI, EEG, genetic and neuropsychological assessments at epilepsy onset may facilitate data-driven approaches to predict drug resistance in individual patients, but this requires concerted effort to set up platforms to established multi-centre robust cohorts, which are currently limited to patients with established epilepsy only.[68] Optimising our ability to predict outcomes including drug resistance, seizure freedom following surgery,[69] developmental trajectories with and without surgery will facilitate informed shared decision-making discussions with children and their parents.[70-72]

Conclusion

Expedited epilepsy surgery prior to drug resistance challenges conventional dogma. However at experienced centers, expedited surgery may result in better seizure outcomes, earlier improvements in quality of life and less time on ASMs for carefully selected patients who are predicted to develop drug resistance. It may also change the natural history of aberrant brain network dynamics and disruption of neurocognitive development associated with ongoing

abnormal oscillatory and seizure activity. Considering the role of surgery as a first-line option for select lesional epilepsies in children (Figure 3), in our opinion, is an approach which may reduce morbidity, and improve neurocognitive outcomes in children with lesional epilepsy.

Competing interests

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Figure legends

Figure 1 Flow diagram of the potential benefits of expedited epilepsy surgery. We hypothesize that the main benefits stem from the reduction of seizure burden and time on ASMs, ultimately resulting in improved outcomes (including quality of life) and health economic benefits.

Figure 2 Illustration of the challenges of robust outcome assessment in expedited surgery trials. (**A**) Traditional patient timeline with regards to epilepsy surgery. The green circle represents seizure onset, red circle represents definition of DRE, yellow circle represents the timing of pre-surgical evaluation (in the best of cases), and the blue circle represents time of epilepsy surgery. (**B**) Patient timelines in the Early Randomized Surgical Epilepsy Trial (ERSET),[73] which compared medical therapy to early surgery soon (< 2 years) after the development of drug resistance, in which both groups were followed up for a similar timeframe of 2 years from surgery or randomization; few patients in the medical therapy arm underwent surgery in this study. (**C**) Challenges of the approach of trying to compare expedited surgery with standard care. As the timepoint of assessment increases from 1 → 4, the proportion of seizure-free patients in the expedited surgery arm is likely to decrease whilst the proportion of those undergoing surgery in the standard care arm is likely to increase (as illustrated in the graph on the right). Ultimately, although we are interested in long-term outcomes, measuring this may be less feasible.

Figure 3 Example of child that underwent expedited epilepsy surgery. He started having episodes of slow laughter followed by confusion, consistent with temporal lobe seizures, at age 13 and was diagnosed with epilepsy 2 months later. At this stage, he underwent an MRI scan revealing a right temporal lesion consistent with a dysembryoplastic neuroepithelial tumour DNET) and was started on Carbamazepine. Despite being seizure free, he was referred to a comprehensive epilepsy surgery centre 3 months after the diagnosis of epilepsy. His seizures recrudesced 8 months after diagnosis and was controlled with an increase in the Carbamazepine dose. He underwent presurgical evaluation.

(**A**) Axial and coronal T2 weighted images obtained as part of epilepsy protocol MRI showing a

right temporal T2 hyperintense lesion consistent with a DNET. (**B**) Interictal EEG showing spike-wave discharges over the right anterior temporal region during sleep on a normal background rhythm. (**C**) Neuropsychological evaluation revealing average performance across all domains of the Wechsler Intelligence Scale for Children (5^{th} UK edition). This was accompanied by average performance in language, memory, visual motor and academic attainment, adaptive behaviour and executive functioning scales.

He was offered surgery 12 months after diagnosis. He underwent a right temporal lesionectomy, sparing the mesial temporal structures, 17 months after diagnosis whilst still on a single ASM. Histology confirmed a DNET. He is seizure free (Engel class 1A) 6 months after surgery.

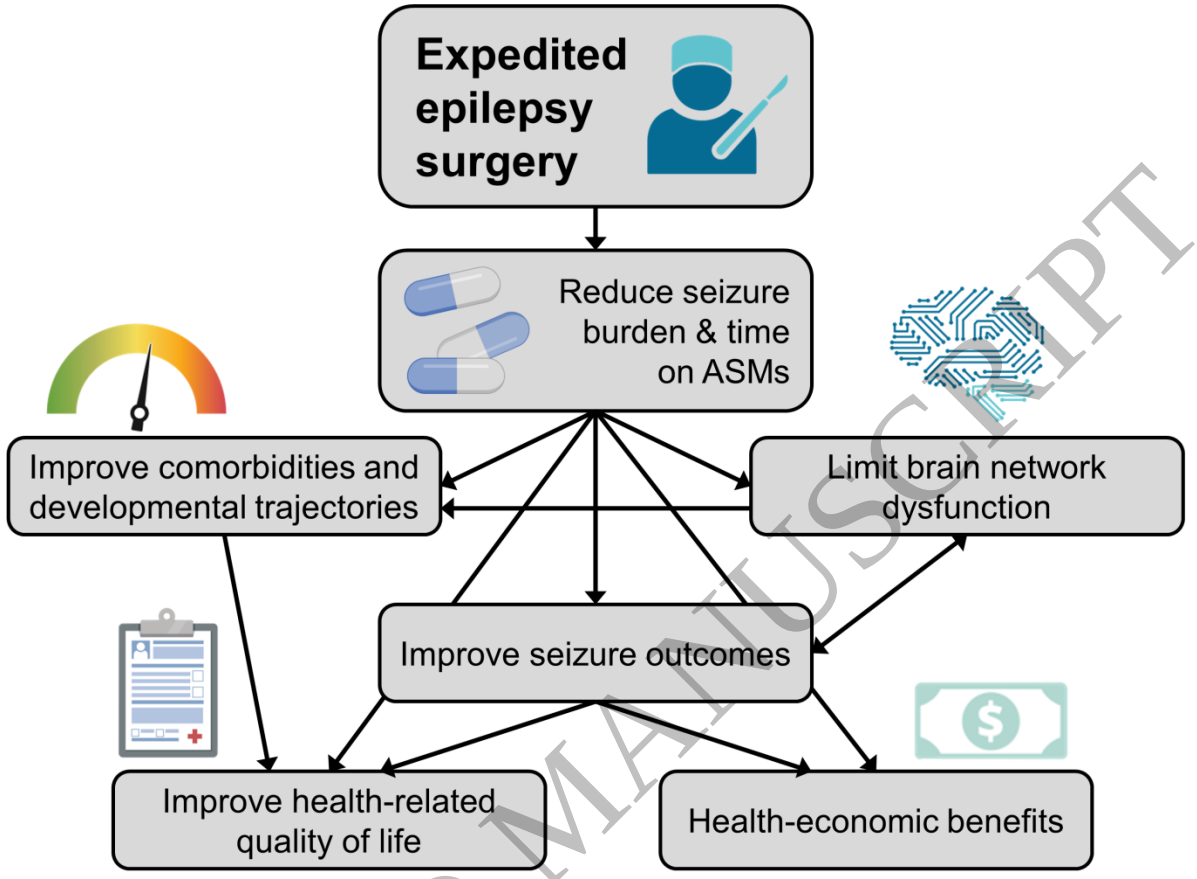

Figure 1
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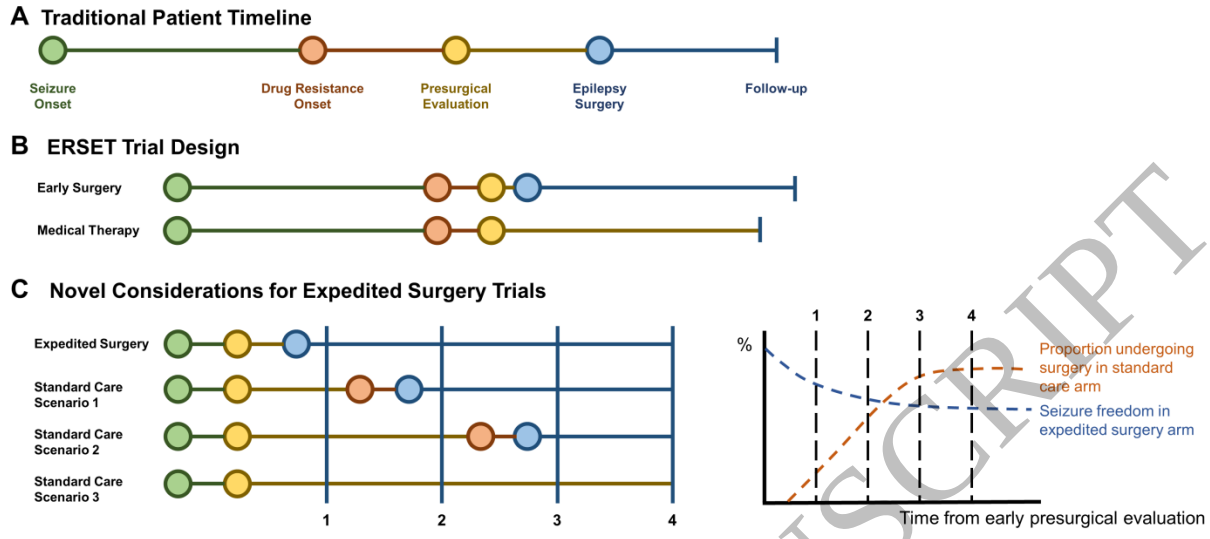

Figure 2
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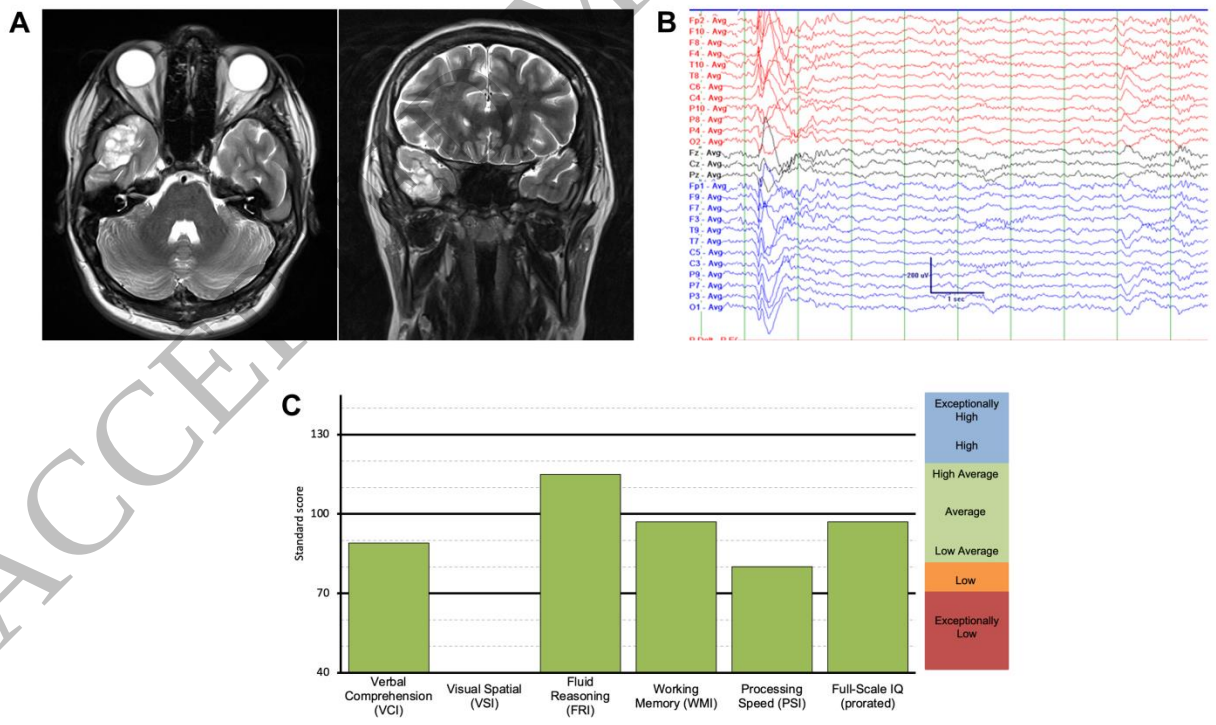

Figure 3
302x178 mm (x DPI)