

## Optimising epilepsy surgery

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One third of individuals with epilepsy do not have seizures controlled with medication, amounting to 20 million people worldwide. Neurosurgical treatment is potentially curative for focal epilepsy. In the most favourable circumstances, over 80% may have a one-year remission, but there is subsequent attrition over 20 years with approximately 40% remaining seizure free.<sup>1,2</sup> Clinical factors assist in predicting the chance of seizure freedom after surgery. Positive factors include the presence of a focal lesion on MRI that is concordant with clinical and EEG data. Negative predictors include normal MRI, extratemporal epilepsy, focal to bilateral tonic clonic seizures, a long duration, learning disability and psychiatric pathology.<sup>1,3</sup>

The primary goal of pre-surgical evaluation is to identify the part of the brain that generates seizures. This is addressed by analysing clinical features, seizure semiology, MRI, scalp EEG, PET and other functional imaging methods. Visual reading of MRI is increasingly supplemented by computational analysis of MRI data with the aim of identifying subtle abnormalities not evident on visual analysis.<sup>4</sup> For neurophysiological data (EEG and MEG) spikes, high frequency oscillations, and abnormality maps of interictal data, alongside ictal recordings have localizing value.<sup>5-7</sup> These methods may guide further evaluation, but are far from perfect and there are issues with false positive detections and the need to balance sensitivity and specificity.

In a personal view in this Journal, Jirsa et al discuss personalized brain modelling to create a virtual epileptic patient (VEP) brain model by combining multiple modalities into a single analysis. The approach uses an anatomical parcellation of structural MRI and structural connectivity derived from diffusion MRI, with the estimates of ictal sources identified with intracranial EEG.

Whilst intracranial EEG is often regarded as the gold standard by which to localize sites of seizure onset and propagation, it must be borne in mind that each recording contact only samples electrical signals from approximately one ml of brain tissue. An implantation of 16 electrodes, each with six contacts, will therefore sample approximately 80ml of brain, 50ml of which will be grey matter, a small proportion of the cortical grey matter. A potential advantage of model-based approaches is the

inference of epileptogenicity of cortical tissue that is not sampled by SEEG contacts to generate hypotheses for the locations of seizure onset and propagation.

The modelling approach comprises a set of equations which describe an approximation of assumed activity of different brain areas in the transition to ictal dynamics. These equations are parameterized by patient data. An open question is how to best use data to parameterize the model, or how to make assumptions. For example, in the current formulation the model is parameterized for seizures to spread preferentially along stronger connections. However, if seizures spread preferentially along more abnormal connections<sup>8</sup> then model performance could be improved further.

Advantages of the VEP modelling framework are the ability to compare, contrast, and test multiple assumptions in the model giving potential mechanistic interpretations. For example, one can simulate multiple surgeries in different locations and extent, then compare them against each other.<sup>9</sup> Furthermore, multiple types of treatment can be simulated such as neuromodulation or alternative medications.<sup>10</sup> Thus, although mainly used for surgery, the framework has the potential for wider application.

The VEP model program is currently being evaluated in a randomized prospective study in which results are made available to treating teams evaluating 356 patients having SEEG for consideration of surgical treatment of drug-refractory focal epilepsy. The results are awaited with interest and will merit careful examination. Questions will include the extent to which treating teams decisions were altered by VEP output, and whether resections may be recommended that were larger than would have been the case, with a risk of a consequent increase in morbidity.

This is a very interesting development that points the way toward more sophisticated AI-based clinical decision support tools for guiding the complex pathways of epilepsy surgery. It is increasingly recognized, however, that focal epilepsy is frequently not driven by a single focus, but is a consequence of an abnormal distributed epileptogenic network. It is, therefore, not surprising that a focal resection may fail to give seizure control. Whilst virtual brain models will be helpful for a subset, this will not be a universal solution. Many lines of enquiry will be needed. Whilst some focal epilepsies will involve a single focus or node that can be cured by resection or ablation, others may need different solutions, such as desynchronization of a distributed epileptogenic network.

## References

1. Bell GS, de Tisi J, Gonzalez-Fraile JC, Peacock JL, McEvoy AW, Harkness WFJ, Foong J, Pope RA, Diehl B, Sander JW, Duncan JS. Factors affecting seizure outcome after epilepsy surgery: an observational series. *J Neurol Neurosurg Psychiatry*. 2017 Nov;88(11):933-940.
2. McIntosh AM, Wynd AW, Berkovic SF. Extended follow-up after anterior temporal lobectomy demonstrates seizure recurrence 20+ years postsurgery. *Epilepsia*. 2022 Oct 21. doi: 10.1111/epi.17440.
3. Jehi L, Yardi R, Chagin K, Tassi L, Russo GL, Worrell G, Hu W, Cendes F, Morita M, Bartolomei F, Chauvel P, Najm I, Gonzalez-Martinez J, Bingaman W, Kattan MW. Development and validation of nomograms to provide individualised predictions of seizure outcomes after epilepsy surgery: a retrospective analysis. *Lancet Neurol*. 2015 Mar;14(3):283-90.
4. Spitzer H, Ripart M, Whitaker K, D'Arco F et al Interpretable surface-based detection of focal cortical dysplasias: a Multi-centre Epilepsy Lesion Detection study. *Brain*. 2022 Nov 21;145(11):3859-3871.

5. Owen TW, Schroeder GM, Janiukstyte V, Hall GR et al. MEG abnormalities and mechanisms of surgical failure in neocortical epilepsy. *Epilepsia*. 2023 Jan 8. doi: 10.1111/epi.17503.
6. Taylor PN, Pappasavvas CA, Owen TW, Schroeder GM et al. Normative brain mapping of interictal intracranial EEG to localize epileptogenic tissue. *Brain*. 2022 Apr 29;145(3):939-949.
7. Zweiphenning W, Klooster MAV', van Klink NEC, Leijten FSS et al. Intraoperative electrocorticography using high-frequency oscillations or spikes to tailor epilepsy surgery in the Netherlands (the HFO trial): a randomised, single-blind, adaptive non-inferiority trial. *Lancet Neurol*. 2022 Nov;21(11):982-993.
8. Keller SS, Glenn GR, Weber B, Kreilkamp BA et al. Preoperative automated fibre quantification predicts postoperative seizure outcome in temporal lobe epilepsy. *Brain*. 2017 Jan;140(1):68-82.
9. Sinha N, Dauwels J, Kaiser M, Cash SS et al. Predicting neurosurgical outcomes in focal epilepsy patients using computational modelling. *Brain*. 2017 Feb;140(2):319-332.
10. Suffczynski P, Kalitzin S, Lopes Da Silva FH. Dynamics of non-convulsive epileptic phenomena modeled by a bistable neuronal network. *Neuroscience*. 2004;126(2):467-84.