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SCIENTIFIC COMMENTARIES

The role of computational modelling in seizure localization

This scientific commentary refers to 'Predicting neurosurgical outcomes in focal epilepsy patients using computational modelling', by Sinha *et al.* (doi:10.1093/brain/aww299).

Epilepsy is one of the most common neurological diseases, affecting between 1–2% of the world's population and is defined by a high probability of recurrent seizures. For pharmacoresistant patients with focal epilepsy, in which seizures originate from a restricted brain area, surgery may be an effective means of controlling seizures. Identification and removal of the seizure focus can be highly successful in some instances. Patients with seizures originating in the mesial temporal lobe or from well-defined lesions can expect seizure-free outcomes in the 60–80% range within the first 5 years after surgery. In neocortical, non-lesional syndromes, however, surgery can have limited efficacy (30–50% seizure freedom rates). Although there are likely multiple reasons for poor outcomes, limitations associated with current EEG interpretation methodologies are often cited. EEG recording of spontaneous seizures obtained from electrodes implanted directly onto the brain surface or into the parenchyma is the most specific localization method available. For this reason, it is often used despite its associated surgical risk and invasiveness. This has resulted in strong motivation to develop new methods of mining EEG data for content that cannot be appreciated with simple visual interpretation. An example of such data mining is the use of high frequency oscillations, or bursts of activity in frequency bands not usually accessible to standard visual review. More recently, attention has focused on extracting and analysing an implied network structure from the EEG data by measuring the cross-site correlation of EEG signals. In this issue of *Brain*, Sinha *et al.* present a patient-specific computational model based on a functional connectivity measure applied to intracranially recorded EEG signals. They use the model to predict postoperative seizure outcomes, and, in cases with poor outcomes, to suggest alternative resection sites (Sinha *et al.*, 2016).

To accomplish this task, the group created a graph representation of the implied neural network for each patient, in which each EEG electrode was a node. Connections between nodes were defined from a functional connectivity measure applied to interictal 1–70 Hz filtered EEG segments free of epileptiform discharges. Although the authors did not describe their calculation in detail, typically such measures involve assessing coherence or cross-correlation of paired EEG signals. The measure produced values ranging from zero (low correlation) to one (high correlation), which were assigned to graph edges linking pairs of nodes. A mathematical model was built from the resulting graph representation, with parameters set so that the oscillatory activity generated by the model at each node took on a bistable characteristic. That is, the activity switched between low amplitude and high amplitude states. In order to assess the likelihood that a node (i.e. electrode site) would seize, the time required for each node to cross into a state of high amplitude oscillations ('escape time') under various noise input scenarios was calculated. Nodes with the shortest escape times were then identified. In aggregate, these nodes defined the proposed cortical resection. A 'virtual resection' was then simulated by disconnecting nodes that corresponded to a proposed resection in the graph representation and rerunning the model to recalculate escape times. A significant change in escape time was considered as an indication of the effect of the proposed resection on overall seizure susceptibility.

To provide validation for the model's predictions, an outcome study was conducted using a dataset of intracranial recordings and post-surgical neuroimaging obtained from 16 patients. Eight patients had good seizure outcomes (ILAE class I–II), and eight had poor outcomes (ILAE class III–V). The model predicted reduced seizure likelihood in seven of the eight cases in the good outcome group, and in two of the eight cases in the poor outcome group. Further, the model proposed an 'optimal' set of electrode sites for resection for each patient. An example was provided in which a multilobar

Glossary

Functional connectivity: The correlation between temporal signals from spatially remote brain regions. Usually determined independently from structural linkages.

Graph, node, and edge: A mathematical construct (graph) representing a set of objects (nodes) and the numerical relationships between them (edges).

Seizure onset zone: The smallest cortical region delineating the sites from which seizures arise, usually determined using EEG recordings from intracranially implanted electrodes

resection region was proposed based on the model's results, in a case where a resection limited to one lobe had resulted in a poor seizure outcome.

This study, together with recent investigations by other groups employing similar methodologies, offers proof-of-principle that a model-based approach can provide an adequate test of a 'virtual resection' in a given patient (Burns *et al.*, 2014; Goodfellow *et al.*, 2016; Khambhati *et al.*, 2016). This is a novel form of personalized medicine, as the model's parameters reflect each patient's unique neurophysiology. These studies suggest that in future, epilepsy surgery planning may be aided by individualized simulations, perhaps similar to the model proposed here.

Another significant contribution is the implication that functional connectivity derived from a limited EEG frequency range is a major determinant of seizure susceptibility. This is an interesting result, as the model entirely excluded several EEG features that are considered to be important biomarkers. These include high frequency oscillations and specific electrographic seizure onset patterns, which tend to be asynchronous in the initial phase of a seizure, as well as other important localizing information such as MRI abnormalities and seizure semiology.

Further investigation is needed, owing to the limitations of the surgical outcome study and the assumptions inherent in the functional network analysis. The most important limitation is that EEG-based measures can identify the presence of correlated activity, but not the physiological circumstance. For example, there are several mechanisms that can explain high correlation values. These include a distribution of synaptic currents from a source that may or may not be recorded, entrainment of oscillations due to normal cognitive processing, pathological or physiological slow waves over an extended territory, and either increased or decreased EEG amplitude. Moreover, at sites left intact after brain resection, these features are likely to be affected in ways that may not be easily predicted. Another consideration is that neuronal firing may be dramatically different at sites that demonstrate aligned oscillations. This has been established during both paroxysmal discharges in an animal model (Prince and Wilder, 1967) and during human seizures (Schevon *et al.*, 2012). The phenomenon is largely due to the inability of EEG in most situations to distinguish between excitatory and inhibitory currents. Thus, the presence of correlated EEG activity at a given pair of electrode sites does not imply that neuronal firing at those sites is also coordinated. Similarly, results can vary significantly based on the choice of model and the parameters used, as described by the well-known quip 'The best material model of a cat is another, or preferably the same, cat' (Rosenblueth and Wiener, 1945). To this point, Sinha *et al.* acknowledged that they tried various parameters, and reported those with the best results. While it is possible that their method is optimized, both careful grounding in physiological principles and testing with an accepted validation technique are critical for demonstrating model robustness and generalizability.

The authors point out that their use of an arbitrarily selected segment of interictal (non-seizure) data implies that long-term invasive recording to capture spontaneous seizures may be rendered unnecessary. This goal relies on the notion that interictal EEG signals carry information that is not available from visual examination of epileptiform discharges and other pathological interictal EEG features, and that is equivalent to the information provided by video EEG recording of clinical seizures. This hypothesis has motivated studies employing a variety of electrophysiological analysis techniques, including MEG or EEG source localization (Knowlton *et al.*, 2006) and interictal high frequency oscillations (Jacobs *et al.*, 2010), with surgical outcome studies providing indirect validation. A direct test, including identification of the specific neurophysiological features involved, has yet to be carried out.

While current clinical practice bases much of the resection decision on the activity observed at the onset of a patient's seizures, the decision is also commonly informed by the locations of interictal epileptiform discharges and other components of the preoperative evaluation such as neuroimaging findings, seizure semiology and classification, and neuropsychological assessments. Therefore, the added value of any new procedure utilizing interictal data should be compared to predictions made from known interictal, imaging, and clinical biomarkers.

Although the results remain preliminary, the findings reported by Sinha *et al.* are nevertheless intriguing and may open the way to new, computationally-based improvements in the surgical treatment of pharmacoresistant focal epilepsy. Additionally, these and similar studies should spur

new detailed investigations into the relationships between elemental brain physiology, clinical EEG recordings and focal seizure susceptibility.

Tahra L. Eissa[1] *and Catherine A. Schevon*[2]
1 *The University of Chicago, Chicago, Illinois 60637, USA*
2 *Columbia University, New York, New York 10032, USA*

Correspondence to: Catherine A. Schevon
E-mail: cas2044@columbia.edu

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A novel animal model offers deeper insights into REM sleep behaviour disorder

This scientific commentary refers to 'Genetic inactivation of glutamate neurons in the rat sublaterodorsal tegmental nucleus recapitulates REM sleep behaviour disorder', by Valencia Garcia *et al.* (doi:10.1093/brain/aww310).

When REM sleep behaviour disorder (RBD) was formally identified in 1986 (Schenck and Mahowald, 2002), its clinical phenotype was recognized as closely mirroring findings from an experimental animal model of RBD reported in 1965 by Jouvet and Delorme of Claude Bernard University in Lyon, France (Schenck and Mahowald, 2002). Bilateral, symmetrical, mediodorsal pontine tegmental ('peri-locus coeruleus alpha nucleus') electrolytic lesions in cats resulted in the permanent loss of 'REM-atonia', one of the defining features of REM sleep along with rapid eye movements and an activated EEG. Lesions to other brainstem structures, removal of the cerebellum, or destruction of the upper vestibular nuclei, had no effect on REM-atonia. These pontine-lesioned cats also displayed *de novo* 'hallucinatory-type' behaviours during REM sleep—in the absence of any environmental stimulation or provocation—that strongly resembled 'oneirism' (dream enactment). The categories of oneiric behaviours expressed during REM sleep in these cats, along with the behaviours not expressed during REM sleep, closely match human RBD. Oneiric behaviours in the cats always occurred during unequivocal REM sleep, with REM sleep retaining all of its defining features (apart from loss of REM-atonia): cortical EEG activation, PGO (ponto-geniculo-occipital) waves, unresponsiveness to environmental stimuli, periodic cycling with non-REM sleep, pronounced myosis, microvoltaic electrical activity of the olfactory bulb, and relaxation of the nictitating membranes. Jouvet and Delorme postulated that the mechanisms responsible for the observed oneiric behaviours had an exclusive origin in the CNS, and were dependent on the disruption of internal neural organization within REM sleep. And now 51 years later, the current Lyon group led by P.H. Luppi at the University of Claude Bernard present in this issue of *Brain* a novel rat model of RBD that deepens our understanding of the neuroanatomy, neurochemistry, and neural circuitry underlying human RBD (Valencia Garcia *et al.*, 2016).

Two fundamental questions addressed

Valencia Garcia *et al.* pursued two fundamental questions related to the pontine SLD (sublaterodorsal tegmental) nucleus (equivalent to the peri-locus coeruleus alpha nucleus in cats, and the subcoeruleus nucleus in humans). First, they asked whether glutamatergic neurons of the SLD are essential for generating REM sleep. Second, they asked if their genetic inactivation was sufficient to produce RBD in rats. This harks back to the original study by Jouvet and Delorme, whose experimental lesions to this region produced RBD in cats.