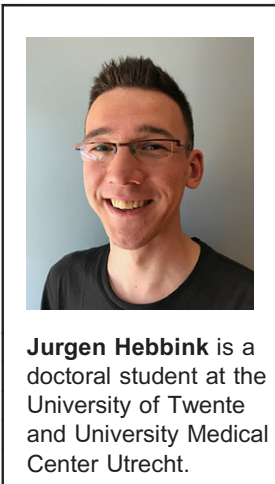




Phenomenological network models: Lessons for epilepsy surgery

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SUMMARY

The current opinion in epilepsy surgery is that successful surgery is about removing pathological cortex in the anatomic sense. This contrasts with recent developments in epilepsy research, where epilepsy is seen as a network disease. Computational models offer a framework to investigate the influence of networks, as well as local tissue properties, and to explore alternative resection strategies. Here we study, using such a model, the influence of connections on seizures and how this might change our traditional views of epilepsy surgery. We use a simple network model consisting of four interconnected neuronal populations. One of these populations can be made hyperexcitable, modeling a pathological region of cortex. Using model simulations, the effect of surgery on the seizure rate is studied. We find that removal of the hyperexcitable population is, in most cases, not the best approach to reduce the seizure rate. Removal of normal populations located at a crucial spot in the network, the “driver,” is typically more effective in reducing seizure rate. This work strengthens the idea that network structure and connections may be more important than localizing the pathological node. This can explain why lesionectomy may not always be sufficient.

KEY WORDS: Focal epilepsy, Network disease, Epilepsy surgery, Computational model.

Epilepsy surgery has provided a cure for patients with focal epilepsy for more than a century now. Success rates remain steady at around 40–60% seizure freedom, although candidates present more challenges nowadays than in the past,¹ when most surgeries were in the mesiotemporal lobe. Many guidelines now stipulate that anyone with focal epilepsy who is resistant to two or more adequately dosed antiepileptic drugs should be considered for epilepsy

surgery. The concepts supporting the effectiveness of epilepsy surgery once seemed straightforward, but have come under scrutiny in light of new research findings, more sophisticated views of brain function, and the enigmatic mechanism in some unsuccessful cases.

Underlying surgery is the idea that the “epileptic focus” should be removed. This was elaborated in the classical articles by Hans Lüders and coworkers,^{2,3} who coined the term “epileptogenic zone” (EZ), defined as the smallest area of cortex the removal of which will lead to seizure freedom. Being an abstraction, it is in practice approximated by the so-called “seizure onset zone,” usually situated within the “irritative zone” of interictally abnormal cortex, showing spikes in the electroencephalogram (EEG). These concepts emerged from experience with intracranial EEG recordings.

This way of thought has recently been expanded with the evolution of magnetic resonance imaging, histological techniques, and classification systems, leading to the belief that surgery is about removing pathological cortex in the anatomic sense, be it an evident lesion, or a microscopical deviation from the normal cortical layering.⁴ Even in normal

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neuroimaging, in this view there should be a cortical substrate. Thus, the abstract EZ is replaced with the idea of a “histologically pathogenic zone.” Surgical failure is then explained as incomplete removal of microscopical abnormalities.

In concurrence with these views, signal analysis led to the idea of epilepsy not as a localized, but as a network disease,⁵ with a collection of “hyperexcitable nodes” in physiological networks. Concepts have been developed, partly from network theory, to describe and quantify these notions. We now speak of an “epileptogenic network,” network “recruitment,” and the development of “dual pathology” or “making the network epileptogenic,” to explain disease progression or describe epileptogenesis. Networks are now also fashionable to explain surgical failures, seizure aggravation, deep brain stimulation, and cognitive dysfunction that cannot be understood with only static, focal abnormalities in mind. Clinicians involved in epilepsy surgery will have to cope with these different views that challenge the framework that Lüders coined long ago. Nonetheless, surgeons operate on epilepsy patients when they see an anatomical abnormality and can pinpoint seizures to a nearby area if this is outside eloquent cortex. Thinking of networks then seems impractical, because resection is ultimately focal.

We are now entering an age of advanced computer models that simulate the known physiological and pathological electrochemical properties of neuronal populations. Such neocortical focal epilepsy models mimic an EEG and show interictal spikes and focal seizures in the same unpredictable way as human epilepsy does. These computer models can account for local tissue properties as well as network influences. They can be personalized^{6–8} and therefore hold promise in counseling the neurosurgeon. At the conceptual level, we think that brain network analyses using such models may offer new ideas and strategies for epilepsy surgery. To illustrate this, we will use a relatively simple model of coupled neocortical “nodes,” showing both normal and seizure-like behavior, that may represent an underlying network model of the conceptual EZ and its surrounding tissue. By systematically studying arrangements of four nodes, we will show how network connections influence the seizure rate and how this might change our traditional views of epilepsy surgery, and raise new opportunities in surgical strategy.

METHODS

Model description

Following others,^{9–11} we consider a phenomenological computational network model consisting of nodes connected via directed edges. Each node models a population of neurons that produces an EEG-like signal. We consider each node in our network to represent a couple of squared centimeters of cortex, so part of a lobe. The dynamics of a node are described by a set of differential equations (see Data

S1). A node can produce two different types of activity, representing interictal and ictal activity. Interictal activity represents “normal” brain activity and is characterized by noisy low-amplitude fluctuations. Ictal activity is modeled as pronounced 3-Hz oscillations, mimicking spike-wave discharges.

The simulated activity of nodes 1 and 2 in Figure 1A show the intrinsic dynamics of a node. Both nodes show alternating periods of interictal and ictal activity that arise without changing model parameters. The transition from interictal to ictal activity is due to stochastic perturbations in the model. The transition probability is regulated by a parameter representing the excitability of a node. Termination of ictal activity is nearly deterministic and regulated by a slow process (see Data S1). In Figure 1A, node 2 is hyperexcitable, which results in more frequent transitions to ictal activity. In the same figure, the effect of coupling is demonstrated; node 4 receives input from node 3. Consequently, node 4 shows ictal activity only if node 3 produces ictal activity.

Study design

We investigate the role of hyperexcitable nodes in small networks and study the effect of surgery in those networks. We study all 218 topologically different network structures on four nodes. For each of these network structures, we consider five networks. In one network, all nodes have normal excitability; in the other four, one node is hyperexcitable. This yields 1,090 different networks. To determine the networks that exhibit seizures, we simulate 5 h of activity for all networks. All well-connected networks with on average more than one seizure per hour are selected, where we define a seizure as three or four nodes producing ictal activity simultaneously.

We then try to decrease the seizure rate in the seizure networks by removing one of the nodes in these networks. The removal of a node thus mimics the effect of tissue removal in epilepsy surgery, and, if successful, would define the EZ. We evaluate the effect of removing a node by simulating the remaining network for another 5 h and count the number of seizures in this new simulation. As the remaining network has three instead of four nodes, we define a seizure in this reduced network as having two or three nodes in ictal state at the same time. Removing a node is only considered if the remaining network has some connections left. Using this procedure, we determine the optimal node to remove to reduce the seizure frequency. We compare this with the effect of removing the hyperexcitable node.

RESULTS

Figure 1 shows simulations for some typical networks. The network in Figure 1B has a reciprocal connection between nodes 3 and 4. We call such a loop a “cycle.” This cycle stabilizes the network. The network in Figure 1C is

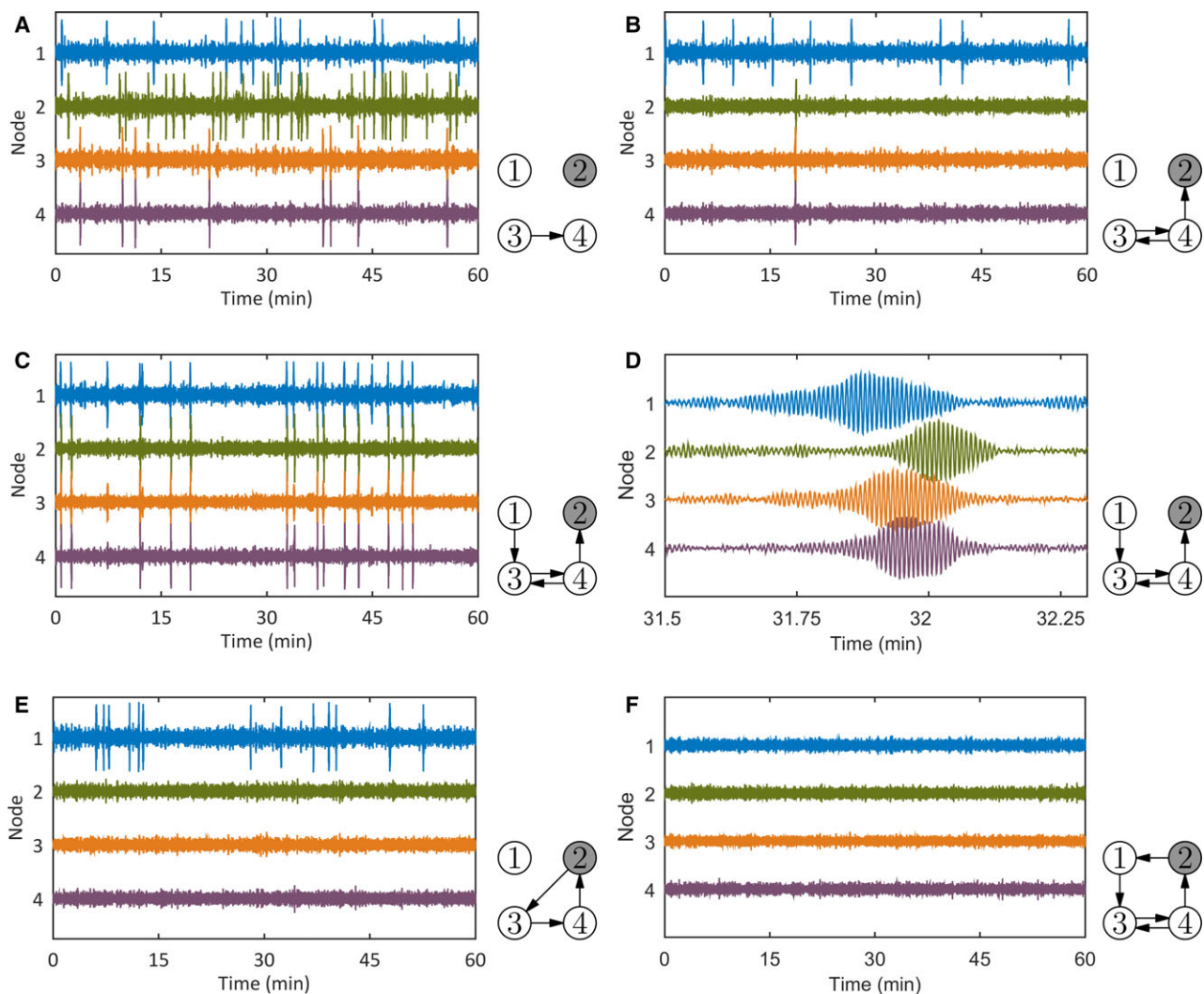


Figure 1.

(A–C, E, F) Simulations of five characteristic networks. The high amplitudes in the signals are periods of ictal activity. In these networks, the gray node (node 2) is more hyperexcitable. (D) Close-up of a seizure of subfigure C. The seizure starts at the driver (node 1) and spreads via nodes 3 and 4 to node 2.

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similar except for an additional connection $1 \rightarrow 3$. This connection causes a large increase in seizure rate. In this network, all seizures start at node 1 (see Fig. 1D), which is a node that does not receive input itself. We will call such a node a “driver.” The networks in Figure 1E,F both contain cycles. Despite the presence of a hyperexcitable node in these cycles, they do not show seizures. This shows the importance of network structure; a hyperexcitable node is not necessarily bad, depending on the location in a network.

We found 387 networks with sufficient seizures, of which 72 do not contain a hyperexcitable node. Histograms of the distribution of seizures are shown in Figure 2. Results suggest a categorization of networks in three classes: networks without a cycle, networks with cycle but without driver, and networks with a cycle and a driver. The networks with a

cycle but without a driver exhibit only a few seizures. Networks in the other classes show many seizures.

Also, the presence of a hyperexcitable node plays a role. The seizure distribution of networks with a hyperexcitable node shows an additional peak (Fig. 2C) of high seizure rate as compared to the networks without such a node. Networks with a cycle only show relevant seizure activity if they contain a hyperexcitable node.

The effect of node removal is shown in Figure 2B,D,E and is usually large in networks containing a cycle and a driver. Most of them become (almost) seizure-free under optimal resection strategy, but not necessarily due to the removal of the hyperexcitable node. The best intervention is to reduce a network to one without a driver (Fig. 2H,I). Intervention may incidentally lead to seizure increase if

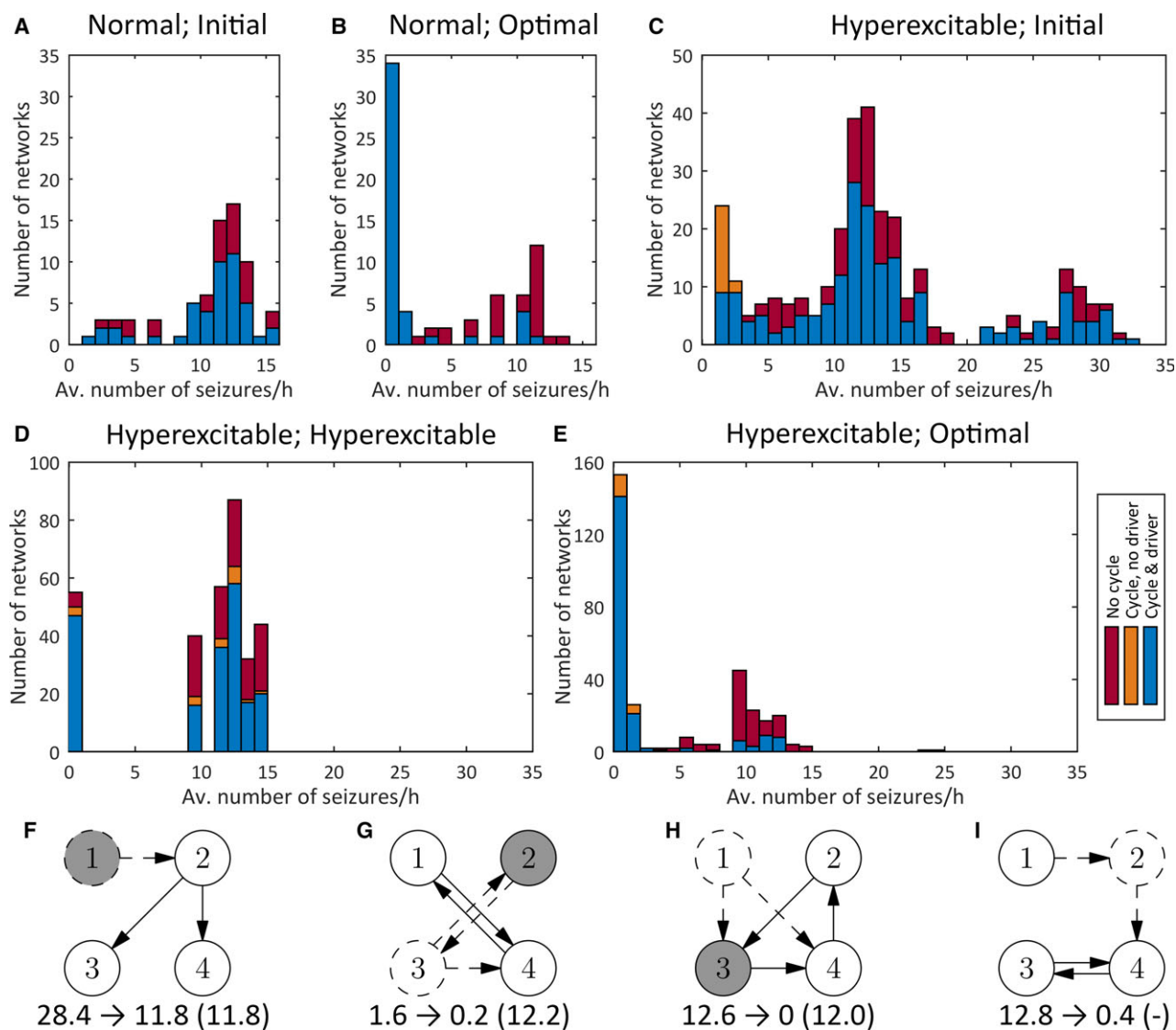


Figure 2.

(A, C) Seizure rate in the original networks for networks without and with a hyperexcitable node, respectively. (B, E) The seizure rate distribution for the optimally improved networks are shown in panel B for normal networks and panel E for networks with a hyperexcitable node. (D) The histogram of the seizure rate distribution after removing the hyperexcitable node. (F–I) Subfigures show optimal improvements in selected networks (indicated by dashed lines). The numbers below indicate initial seizure rate → seizure rate after optimal improvement (seizure rate after removal of hyperexcitable node). Optimal improvements in all other networks can be found in Data S2.

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removal of the hyperexcitable node in a cycle creates a driver, as in Figure 2G.

Node removal in networks with a cycle but without a driver yields only a small decrease in seizure rate from their originally low seizure rate. Networks without a cycle cannot become seizure-free and show in general little improvement. Only when they have a hyperexcitable node as a driver and show an extremely high seizure rate will removal or isolation of the hyperexcitable node decrease the seizure rate drastically (Fig. 2F).

DISCUSSION

Our work suggests that the notion of network structure and connections may be more important than localizing the pathological node. Our model shows that removal of normal driving nodes, located at a crucial site within the network, is effective in preventing seizures, and would constitute the EZ in such a case. At the same time, removal of the abnormal hyperexcitable node in the same network does not always help. Local hyperexcitability thus does not seem to

be an obligatory feature of the EZ in network dynamics. This may help to understand the success of anteromesial temporal lobe surgery, in which the hippocampus may be such a driver. Removal of the hippocampus has become key to the effect of temporal lobe surgery, even in neocortical cases. It may also explain why lesionectomy in itself may not be sufficient, as a nonpathological driver in a network cycle may still remain.

Of course, computational models are a simplification. In our model, the dynamical repertoire of a node comprises an interictal and an ictal state. We assume that each single node may produce ictal activity. The intrinsic dynamics of a single node cannot be measured *in vivo*, as it is influenced by other nodes. Only in the case of *in vitro* brain slices can the dynamics of a single node be observed. It has been reported that such slices will produce spontaneous epileptiform activity.^{12,13} The node dynamics can be made more sophisticated and realistic by using physiologically detailed neural mass models, which have been designed to describe a variety of activities as observed in EEG signals.¹⁴

A promising development is to tailor this approach to individual patients, for example, those undergoing chronic invasive EEG monitoring, by using a patient-specific network model. Such networks can be derived from EEG data using functional connectivity measures, for example, correlation or Granger causality. Information about local cortical excitability can be incorporated in the node parameters. The effect of removal of certain cortical areas could then be predicted using the computer,^{6–8} and this could be compared to clinical effect in a prospective study.

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DISCLOSURE

The authors declare no conflicts of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Data S1. Detailed description of the computational model.

Data S2. Overview of all selected four node networks.