Epilepsy surgery: Evaluating robustness using dynamic network models

Junges, Leandro; Woldman, Wessel; Benjamin, Oscar; Terry, John

Citation for published version (Harvard):
Junges, L, Woldman, W, Benjamin, O & Terry, J 2020, 'Epilepsy surgery: Evaluating robustness using dynamic network models', *Chaos*, vol. 30, no. 113106.

Epilepsy Surgery: Evaluating robustness using dynamic network models

Leandro Junges[1,2,*,a], Wessel Woldman[1,2,*], Oscar J. Benjamin[3], John R. Terry[1,2]

Affiliations

[1] Centre for Systems Modelling and Quantitative Biomedicine, University of Birmingham, Birmingham, B15 2TT, United Kingdom.
[2] Institute for Metabolism and Systems Research, University of Birmingham, Birmingham, B15 2TT, United Kingdom.
[3] Department of Engineering Mathematics, University of Bristol, Bristol, BS8 1UB United Kingdom.
* Denotes equal contribution as first author.
[a] Corresponding author: l.junges@bham.ac.uk.

Abstract

Epilepsy is one of the most common neurological conditions, affecting over 65 million people worldwide. Over one third of people with epilepsy are considered refractory: they do not respond to drug treatment. For this significant cohort of people, surgery is a potentially transformative treatment. However, only a small minority of people with refractory epilepsy are considered suitable for surgery and long-term seizure freedom is only achieved in one half of cases. Recently, several computational approaches have been proposed to support presurgical planning. Typically, these approaches use a dynamic network model to explore the potential impact of a surgical resection *in silico*. The network component of the model is informed by clinical imaging data and is considered static thereafter. This assumption critically overlooks the plasticity of the brain and therefore how continued evolution of the brain network post-surgery may impact upon the success of a resection in the longer term. In this work, we use a simplified dynamic network model, that describes transitions to seizures, to systematically explore how network structure influences seizure propensity, both before and after virtual resections. We illustrate key results in small networks, before extending our findings to larger networks. We demonstrate how evolution of brain networks post resection can result in a return to increased seizure propensity. Our results effectively determine the robustness of a given resection to network reconfiguration and so provide a potential strategy for optimising long-term seizure freedom.

Brain surgery is a potentially life-changing treatment for people with epilepsy that do not respond to drug therapy. Unfortunately, identifying brain regions responsible for seizure generation and spread is complex and so the number of people considered suitable for surgery is relatively low and outcomes are non-optimal. Many people for whom surgery appears initially successful see seizures return within a year or so. Several computational methods that combine network analysis and mathematical modelling have been proposed lately to support surgical planning by evaluating virtually the potential impacts of a surgical resection. In such models, representations of brain networks are extracted from clinical data. However, these methods typically consider brain networks to be static after surgery, ignoring the potential effects of network reorganization in long-term seizure freedom. In this work we use a dynamic network model of seizure transition to systematically evaluate the influence of network structure in seizure propensity before and after virtual resections. We use small networks to illustrate how a successful resection can be adversely influenced by post-surgical network reconfiguration, where the creation or destruction of network edges lead to an increase in seizure propensity. We then

extend our results to networks with sizes more in line with what is typically obtained from clinical data. The results presented in this work shed light upon the issue of brain networks sensitivity to reconfiguration, and provide a framework to evaluate the robustness of therapeutic interventions. This framework can potentially be used more generally to explore robustness in the behaviour of dynamic coupled systems.

I. Introduction

Epilepsy is a very common serious primary neurological condition[1]. Epilepsy is characterised by the tendency to have spontaneous seizures[2]. In some cases, the cause of seizures is readily apparent (e.g. a brain tumour or cortical lesion), however for the majority the definitive cause is unknown. With appropriate treatment, approaching two-thirds of people with epilepsy have well-controlled seizures[3]. For the remaining third, more invasive therapies including electrical stimulation[4] and surgery[5] are potential options. For those people with epilepsy for whom surgery is considered appropriate, long-term seizure freedom is achieved in around 50% of cases. However, success rates may be as high as 80% where an affected brain region is clearly identifiable, but as low as 15% in cases where no such brain region is apparent[6]. A further consideration is the lasting impact of the surgery. Many people with epilepsy display a reduction in seizure rates immediately after surgery, however their seizures often return over time and may be different in nature to those with which they were initially diagnosed[6,7]. Despite these challenges, epilepsy surgery has been shown to be a highly cost-effective solution[8] and many believe it should gain more widespread acceptance as an alternative treatment for people with refractory epilepsy[9,10].

One explanation for this wide variation in surgery success rates is the role of large-scale brain networks in seizure generation, which has become increasingly recognised in recent years[11–16]. This recognition has resulted in the International League Against Epilepsy updating its operational classification of seizure types to reflect the role networks play in the generation of seizures[17]. Clinically, brain networks can be characterised through structural or functional relationships. Structural connections essentially represent the anatomical links between brain regions as typically measured using magnetic resonance imaging (MRI). These structural links are hypothesised to form the basis of functional connections between brain areas. Typically, functional connections are inferred statistically from time-series data such as functional MRI, electroencephalography (EEG), or magnetoencephalography (MEG) (see Stam[18] for a comprehensive review).

However, as van Mierlo and colleagues observed[16]: "*With the growing enthusiasm for connectivity it is often overlooked that in reality, all we have are statistical interdependencies of signals, which should be interpreted cautiously.*" Because of the largely qualitative nature of these clinically defined networks, there has been considerable interest in the development and application of mathematical methods, notably from network science and dynamical systems, to better understand seizure generation and therefore the condition of epilepsy[19]. For example, in early work[20] a dynamic network model was constructed to demonstrate that emergent activity characteristic of different seizures types could arise due to changes in either the edge structure of the network, or the dynamic activity within nodes. The dynamics within each node of this model are determined by a bistable switch that characterises transitions between phenomenological representations of healthy (background) and pathological (seizure) states. Based upon the normal form of a sub-critical Hopf bifurcation, this class of model was first introduced in the context of epilepsy by Kalitzin *et al.*[21] and Benjamin *et al.*[22]. Although a gross simplification of the brain, the model provided insight as to why loss of connections between brain regions made the brain – on average – more seizure prone. Many subsequent approaches

have since built on this concept of seizures as an emergent property of the interplay between nodes within a network and its connectivity (see Milton[23] for a classical introduction and Moraes *et al.*[24] for a recent review).

A number of approaches have recently been developed that combine clinical data with mathematical models to understand surgical strategies or to inform pre-surgical planning. For example, a computational study[25] identified differences between structural brain networks of people with temporal lobe epilepsies and healthy controls. They further showed that measures of seizure rates (as calculated from the model) could be lowered by removing certain nodes within the network. In 2016, Goodfellow *et al.*[26], undertook the first study that utilised intracranial EEG (iEEG) recordings, alongside pre- and post-operative imaging, to predict *in silico* the effects of removing macroscopic regions of the cortex in the emergence of epileptiform activity. Key findings of this study were replicated using a bistable dynamic network model in work by Sinha *et al.*[27]. Khambhati *et al.*[28] simulated cortical resections in virtual brain networks obtained from electrocorticography, and suggested a *push-pull* control effect resulting from a competition between synchronizing and desynchronizing network regions which influence seizure spread. Jirsa *et al.*[29] have developed a computational approach to support brain surgery based on non-invasive structural data (the *Virtual Epileptic Patient*). Lopes *et al.*[30] used iEEG recordings to show that scale-free and rich-club functional brain networks have specific nodes that are central for seizure generation and, therefore, should be targeted in resective surgery.

Whilst these approaches have shown promise, it is very important to consider the implications of the assumptions underlying both epilepsy surgery and the models with which predictions of outcome are made. One critical assumption is that the perturbation to the brain as a consequence of the surgery is ever lasting. However, there is no reason to assume that connections between remaining regions of the brain stay static post-surgery. On the contrary, the brain is highly plastic[31] and evidence of ongoing changes are supported by the clinical observations of declining seizure freedom over time in people who have undergone apparently successful surgery[6,7]. A further challenge is that we do not know *a priori* how best to mathematically characterise brain dynamics that underpin the emergence of seizures within a dynamic network. Recent work[32] has demonstrated that predictions of the outcome of surgical strategies may depend on the choice of mathematical model that defines the behaviour of each node within the network.

Collectively these issues relate to dynamic robustness. By this we mean how do ongoing dynamic factors impact upon the choice of perturbation that we might make. This is an important consideration in the context of epilepsy surgery. For example, there may be multiple routes to achieving apparent seizure freedom, however some may be more dynamically robust than others. In this work we evaluate how network topology influences seizure propensity, and quantify the effects of virtual surgical resection, represented by the removal of network nodes. Finally, the results are extended to larger networks, more in line with measures obtained from clinical data.

II. Methods

A. Dynamic Network Model

We consider a bistable dynamic network model that can generate both healthy background-like and seizure-like activity at a phenomenological level[21,22]. Activity within each brain region is described by a modified version of the normal form of the subcritical Hopf bifurcation, with an additional equation to describe slow variations of the "excitability" variable λ[22,33]:

$$\frac{dz_j}{dt} = z_j(\lambda_j - 1 + i\omega + 2|z_j|^2 - |z_j|^4) + \frac{\beta}{N}\sum_{k=1}^{N} A_{kj}(z_k - z_j) + \alpha dW_j \quad (1)$$

$$\tau\frac{d\lambda_j}{dt} = \lambda_{j0} - \lambda_j - |z_j|^2 \quad (2)$$

where $j = 1, \ldots, N$ represent the network nodes. These coupled stochastic differential equations describe the evolution of complex variables z, where the coupling is linear and proportional to the difference between node states. The real part of the state variables can be thought of as a proxy of the electrographic activity of a brain region, for example as measured using EEG. In this framework, network nodes are associated to regions of the brain generating the electrical signal measured by the EEG electrodes. When $\lambda_j \in [0,1]$, there are two distinct dynamical behaviour: low-amplitude noisy activity near the origin (stable fixed point $z = 0$) and large amplitude, oscillations (stable limit cycle at $|z|^2 = 1 + \sqrt{\lambda}$). These two stable attractors are separated by an unstable limit cycle (located at $|z|^2 = 1 - \sqrt{\lambda}$). At a phenomenological level, the stable fixed point can be thought of as "background-like" activity as observed in electrographic recordings, whereas the stable limit cycle corresponds to "seizure-like" activity. For large enough noise, the system will eventually transition into the seizure-like state, after which the slow variable decreases (past the limit point located at 0) and the system will return back (with time-scale τ) to the background-like state.

Consequently, this phenomenological model provides a framework in which one can systematically examine how different model components (e.g. noise, network structure, baseline excitability, coupling strength) impact the propensity of seizure-like activity. Full details of model variables and parameters are provided in Tables 1 and 2.

Variable	Interpretation	Dimension
z_j	Complex activity variable of node j	2 x N
λ_j	Excitability of node j	N
W_j	Complex Wiener process	2 x N

Table 1: Model variables.

Parameter	Interpretation	Typical range	Value
N	Number of nodes in the network	3-10	4
ω	Frequency of the stable limit cycle	3-50	20
β	Coupling strength between nodes	0.05-6	-
α	Noise strength	0.005-0.10	0.08
τ	Time-scale of the slow variable λ	5-50	5
λ_{j0}	Baseline level of excitability	$\in [0,1]$	0.75
A	Adjacency matrix	1 (connection), 0 (no connection)	-

Table 2: Model parameter values[33].

An example of the dynamics observed in a network with 4 nodes is shown in Fig. 1. The phase diagram (Fig. 1B) shows that the system spends most of the time near the fixed point $z = 0$. In this regime the simulated EEG activity ($Re(z_j)$) remains in the background state (low amplitude noisy oscillations on the panels on the right). Eventually, the trajectory crosses the boundary of the basin of attraction of the fixed point (dashed line) and transitions into the seizure-like state. A drop in the excitability variable

λ follows (see equation 2) and the system is brought back to the proximity of the fixed point (the background state).

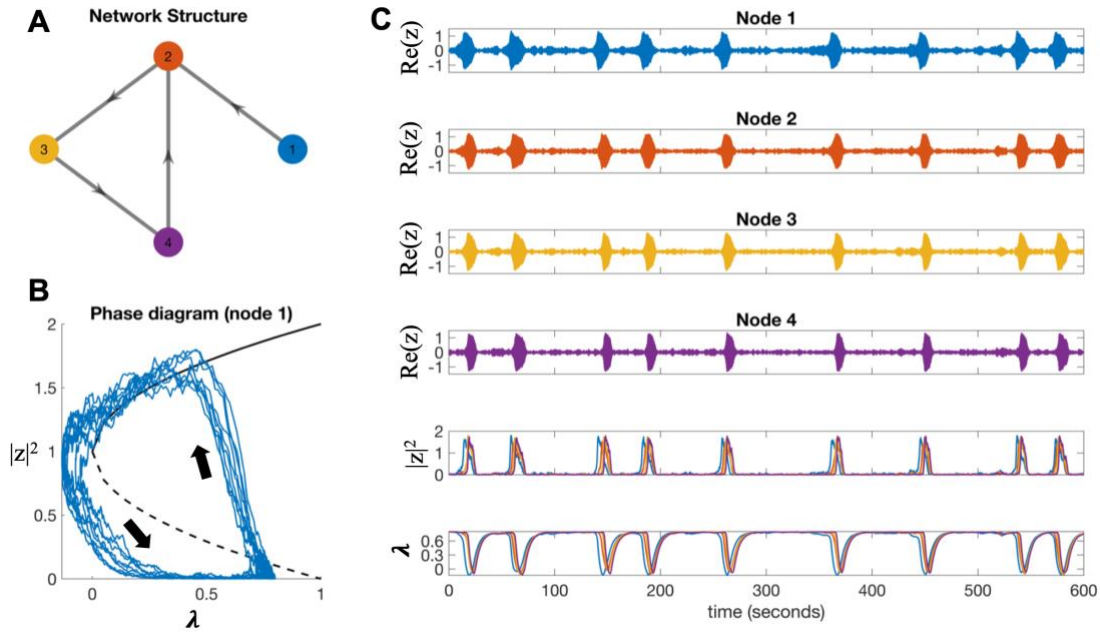

Fig. 1: Example of network dynamics for a 4-node network. (A) Specific network structure. (B) Trajectory in phase space for node 1 (other nodes display similar patterns). The direction of the flow is anti-clockwise (see arrows). (C) simulated electrographic (e.g. EEG) activity ($Re(z_j)$) for the four nodes, amplitude of the complex activity variables ($|z_j|^2$), and slow excitability variables (λ_j). Note that all nodes transitioned simultaneously into the seizure-like state (synchronization). All simulations were carried with an Euler-Maruyama scheme with $dt = 0.0001$. See Table 2 for default values for the model parameters.

For certain classes of coupled bistable systems with noise-induced transitions, it is be possible to analytically examine the behaviours of these systems, for example, derive analytical expressions for the escape time using the Eyring-Kramer equation[34,35]. These escape times have been shown to correlate with seizure propensity[22,36]. In general, however, these high-dimensional dynamic network models do not allow for such analytical treatment and numerical simulations can provide insight into how different mechanisms contribute to seizure propensity.

B. Brain Network Ictogenicity

Recently, several works have used the concept of *Brain Network Ictogenicity* (*BNI*) to estimate the propensity of a network to generate what we term seizure-like activity[36,37]. For example identifying optimal resection regions in epilepsy brain surgery[26,27,30], to classify focal and generalized epilepsies[39], and to assess lateralization in focal epilepsy[40].

Broadly speaking, *BNI* can be thought of as the proportion of time that nodes within a network spend in a seizure-like state. The propensity of seizure-like activity critically depends on the interplay between a number of model parameters. In particular the coupling strength (β), noise strength (α), the time-constant of the slow variable (τ), the network topology (for example, whether it is strongly or weakly connected, the presence of cycles) and the baseline excitability (λ_{j0}). For example, if the baseline excitability λ_{j0} is close to 0, low values of noise strength α are unlikely to lead to seizures whereas if λ_{j0} is close to 1, the same strength of noise would lead to several seizures. In practice the calculation of *BNI* can be implemented in several different ways and depends on many factors, including the specific dynamical model, the precise definition of what characterizes a seizure in this

system, the details of the state transition, model parameters, and coupling type, amongst others. Despite these many factors, the value of *BNI* calculated using different models is often similar[30,32].

An important consideration when calculating *BNI* is to define what constitutes a seizure within the context of the model. For the model we consider, there are two stable attractors, which correspond to a background state and a seizure-like state, and therefore we can use the separatrix as a threshold for whether a node is in the seizure-like state. The details on how such a threshold is defined are often omitted, in spite of the fact that this threshold often has an influence on the absolute values of the *BNI*.

In this study we are primarily interested in the effect of the network structure on seizure propensity, we focus on when seizure-like activity across multiple nodes is driven by the connectivity between them. Consequently, the *BNI* for a given dynamic network structure is quantified by evaluating how long two or more nodes are simultaneously in the seizure-like state (this means that if a single individual node is in the seizure-like state whilst the other $N-1$ nodes are in the background state, we do not consider this to be a seizure).

To quantify the BNI for a given simulation of the dynamic network model, we start by finding all segments in the simulation where at least two nodes are simultaneously in the high-amplitude seizure-like state $\left(|z_j|^2 > 0.5\right)$. The *BNI* is defined as the total sum of the lengths of these segments, scaled by $m/(T_s N)$, where m is the number of nodes in the seizure-like state in each segment ($m \geq 2$), T_s is the total simulation time and N is the total number of nodes.

Consequently, it holds that $BNI \in [0,1]$, where a value of 0 means there was no synchronised seizure-like activity in the simulation, whereas a value of 1 means that all nodes were in the seizure-like state for the entire simulation. See Fig. 2 for a simple example of how the BNI is calculated for a given dynamic network model.

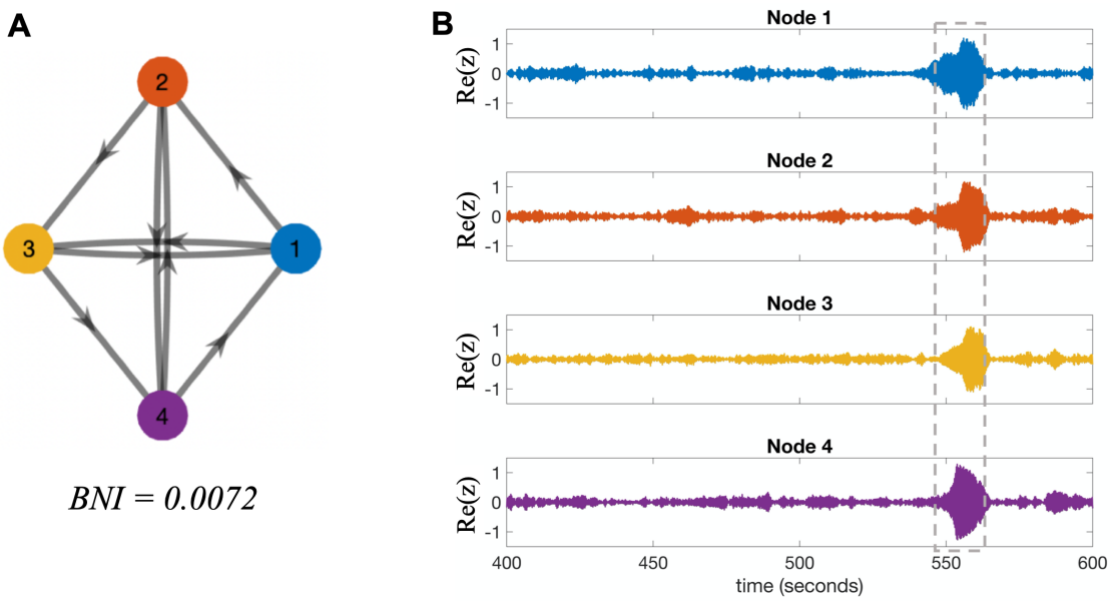

Fig. 2: The *BNI* calculated for a four-nodes network. (A) directed, unweighted network consisting of four nodes. (B) simulated electrographic recording. This simulation contained one segment for which at least 2 nodes have $|z_j(i)|^2 > 0.5$ (dotted box at approximately 550 seconds). Model simulation with: $\beta = 0.20$, $T_s = 1000$; Euler-Maruyama scheme with $dt = 0.0001$; initial conditions: $z_j(0) \approx 0$ and $\lambda_j(0) \approx \lambda_{j0}$, for all other default values see Table 2.

Systematic explorations of the key parameters allow one to extend the BNI as a high-dimensional integral for a given network structure. Fig. 3 shows the dependence of seizure propensity to the choice of parameters of the dynamic network model. Even though small changes in parameter values seem to lead to smooth, monotonic changes in the BNI, this suggests it is in general important to consider the certainty of parameter inference in networks of dynamic models as this could significantly impact the higher-level model outputs of interest.

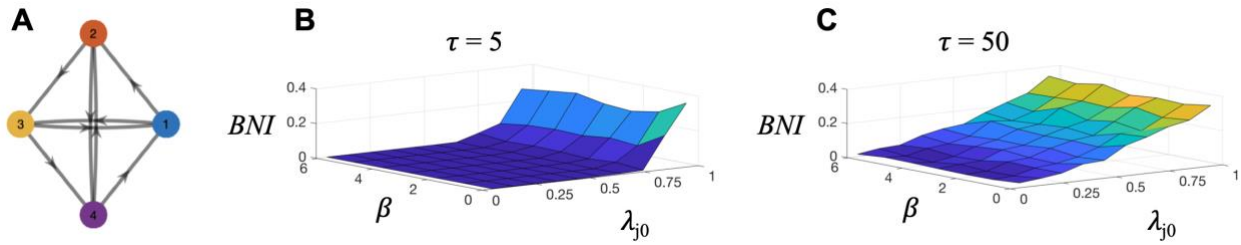

Fig. 3: Seizure propensity (as quantified by *BNI*) depends on the coupling strength β, baseline excitability λ_{j0} and the slow time-scale τ. The *BNI* landscape computed for a given network structure (A) for different values of β and λ_{j0}. (B) $\tau = 5$; (C) $\tau = 50$. All simulations with total simulation time: $T_s = 1000$, using an Euler-Maruyama scheme with $dt = 0.0001$; $\alpha = 0.08$. Initial conditions: $z_j(0) \approx 0$ and $\lambda_j(0) \approx \lambda_{j0}$.

C. Perturbations to network structure

To explore the effect of changes to network topology, such as the removal of a node or the addition or removal of an edge, we start with network structures with four nodes. Initially, we only consider network structures that are at least weakly connected, which guarantees there are no disconnected nodes or subgraphs. If a network perturbation renders the network disconnected, the *BNI* of the perturbed network is determined by the connected component with the largest *BNI*.

In order to consider all potential types of behaviour for a given network structure, we do not restrict our analysis to a single value of the coupling parameter. The *BNI* is averaged over a wide range of values for β (see Table 2), covering all from weak to strong coupling relative to noise and excitability. Additionally, in this work we are not concerned with absolute values of the seizure propensity, which can be influenced by the baseline excitability (λ_{j0}), the timescale of the slow variable (τ), or the noise (α); but with the difference between the *BNI* before and after a network is perturbed, either by a node removal or by network reconfiguration. Therefore, a consistent choice for these parameters is sufficient to reveal the influence of network perturbations in seizure propensity. For the choices of fixed parameters please see Table 2.

III. Results

To understand the impact on network ictogenicity of virtual resections, and how this is further impacted by continued reorganization of the remaining network, we begin by performing a systematic analysis of networks with four nodes. We first establish the relationship between network structure and *BNI* for the given choice of fixed parameters in Table 2. We use this understanding to measure the change in *BNI* upon removal of individual nodes within different network structures, focussing on cases where the original network has high *BNI*. This focus is motivated by the potential clinical application, where such networks might be potentially suitable for surgical intervention. The impact of ongoing network reorganisation post virtual resection is evaluated by considering all possible individual edge changes in an exemplar network. We find examples where removal of a node results in a network with low *BNI* – the desired outcome – however, creating or removing individual edges

results in a dramatic increase in *BNI*. Finally, we show how this effect can also manifest in larger networks, more in line with brain networks obtained from clinical data.

A. Network ictogenicity for 4-nodes networks

There are 199 non-isomorphic networks with four nodes that are weakly or strongly connected. In Fig. 4(A) we present calculations of the *BNI* where networks are sorted by increasing number of edges and, within each edge group, by decreasing value of *BNI*. By comparing the *BNI* values for networks with 3 or 4 edges, and those with 10, 11 and 12 edges, we observe a tendency for networks to present, on average, decreasing *BNI* as the number of edges in the network increases. For networks with 4 to 9 edges, the proportion of networks with relatively low values of *BNI* similarly grows with increasing number of edges. This behaviour is due to the nature of the coupling between nodes within the network (linear and proportional to the difference between node states), whereby a connection from node A to node B results in node A influencing node B to behave in the same way. Combined with node dynamics being brought back to the background state with time-scale τ following transition to the seizure-like state, this makes network nodes hold themselves more strongly in the background state when there are more connections within a network.

However, it is important to recognise that *BNI* does not decrease monotonically with increasing number of edges. Rather, the effect of the network topology, and the hierarchy of the network in particular, plays an important role. Interestingly, all edge groups in Fig. 4(A) present a similar pattern on how the *BNI* decreases. Within each group, networks with relatively high *BNI* are those with a single "driving" node (e.g. a node with no in-connections). An example of such a network is presented in panel N_1 of Fig. 4 (6-edges network with highest *BNI*). In this example, node 2 is not being influenced to remain in the background state by any other nodes, and when it transits to the seizure-like state, it forces nodes 1, 3 and 4 to the same state, leading to a relatively high seizure propensity. The network in panel N_2 considers a case with two driver nodes (2 and 3) which are connected to nodes 1 and 4. Nodes 2 and 3 have a similar influence here as node 2 in network N_1. When both nodes transit to the seizure-like state together, they force nodes 1 and 4 to the same state. However, in the case where one node is in the seizure-like state and the other remains in the background state, they exert opposite influences upon nodes 1 and 4. This competition leads to intermediate values of *BNI* for networks with this general structure. Finally, network in panel N_3 is strongly connected and all nodes tend to hold each other in the background state, resulting in low values of *BNI*.

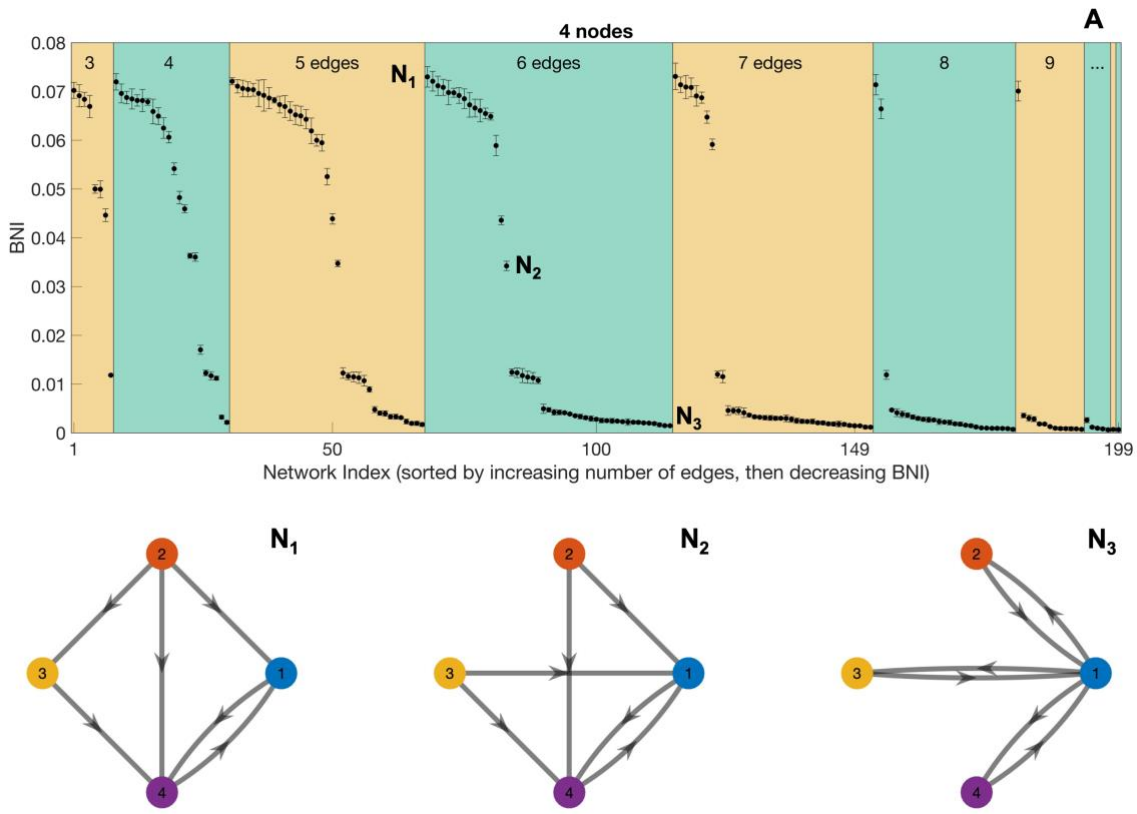

Fig. 4: (A) *BNI* for all networks with 4 nodes, sorted first by increasing number of edges (between 3 and 12), then by decreasing *BNI*. Exemplar 6-edges networks are presented for high (N_1), intermediate (N_2) and low (N_3) values of *BNI*. Error bars represent variations due to noise.

B. Effects of node removal

Epilepsy surgery aims to reduce seizure propensity through the removal of cortical tissue considered key to generating seizures[41]. Within the context of our dynamic network model, we explore this through systematic removal of individual nodes and studying the impact on the level of *BNI* as a result. Nodes identified as being essential to the emergence and/or spreading of seizure-like activity would represent the best candidates for surgical resection. It is important to note on the other hand that some nodes may influence emergent dynamics in such a way as to prevent the spread of seizures, and the removal of such nodes might lead to even more seizures.

To consider these issues Fig. 5(A) illustrates the distribution of *BNI* before and after the removal of each node individually for a given four-node network. The diagonal line separates the cases where the *BNI* after node removal is smaller than before (blue region) from the cases where a removal leads to a remaining network with higher *BNI* (red region). The networks clustered on the left side of the figure have a low *BNI* and any intervention either leads to a similar or higher *BNI*. On the opposite side, networks with high *BNI* are those potential candidates for node removal in order to try to reduce the overall seizure propensity. However, not all networks can lead to lower *BNI* by node removal. From the 58 networks clustered in the region of high *BNI* before node removal ($BNI > 0.055$), 37 (63.8%) have at least one node removal that leads to a network with significantly lower ictogenicity ($BNI < 0.020$). From the 232 possible node removals (58 networks × 4 nodes), only 45 (19.4%) lead to a significant reduction in *BNI*.

Two exemplar networks with high *BNI* are shown in Fig. 5 (N_1 and N_2). The removal of nodes 1, 3 or 4 in the network in N_1 lead to networks with *BNI* very similar to the complete network. However, the removal of node 2 (a driver node) leads to a significant reduction in *BNI*. From a model perspective, this would represent a suitable candidate for therapeutic resection for controlling seizure activity. Conversely, network N_2 also have a relatively high *BNI*, however in this case no node removal lead to a substantial reduction in *BNI*. Here, node removal is not an efficient alternative to reduce network ictogenicity.

C. Robustness to connectivity changes

A critical question to consider is the impact of ongoing network reorganisation following the removal of a node or nodes within the network. Effectively, this is an issue of robustness of a network with respect to increases in *BNI* when edges are either added or removed. To consider this, we evaluate the effect of all possible configurations involving adding or removing a single edge in the remaining network. In Fig. 6 we present an example where network reconfiguration post-removal of a node has a dramatic influence on the level of *BNI*.

The starting network presented in Fig. 6(A) has a relatively high *BNI*. As shown in Fig. 6(B), removing nodes 2, 3 or 4 do not result in a significant change in *BNI*. On the other hand, the removal of node 1, which results in the network presented in panel C of the same figure, significantly reduces *BNI*, suggesting this is a suitable candidate for therapeutic intervention. However, if we add or remove a single edge in the remaining network, which would lead to one of the networks presented in panels D, E and F (all other possible combinations are isomorphic to one of these networks), the *BNI* increases to levels similar to those observed prior to node removal (network in panel A).

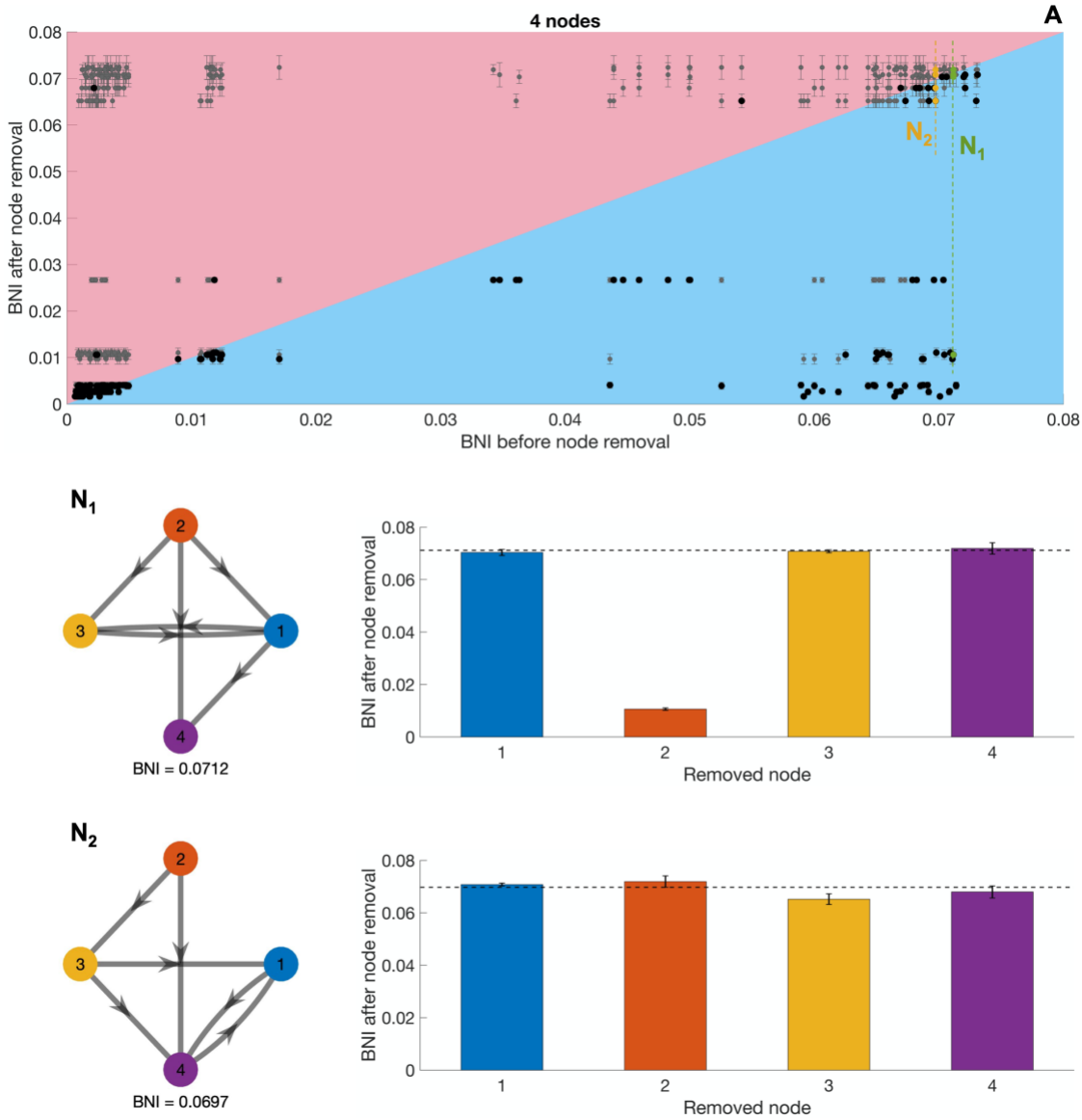

Fig. 5: (A) *BNI* before and after all possible node removal (four one-node removal). Minimum *BNI* after node removal is shown in black, others are shown in light grey. Region in blue (red) indicate a decrease (increase) in BNI after node removal. (N_1 and N_2) Exemplar networks of high *BNI*, with the respective values of the *BNI* after node removal for all nodes individually. Dashed lines represent *BNI* before node removal. The dots associated to networks N_1 and N_2 in panel A are shown in green and yellow, respectively.

This effect is due to the fact that after node 1 was removed, the remaining network has two "competing drivers", similar to the situation described in Fig. 5(N_2). This competing influence results in a lower value of the *BNI*, however this configuration is quite unstable. The addition or removal of any edge breaks up the symmetry between the competing elements and a single driver takes over, bringing the *BNI* up again.

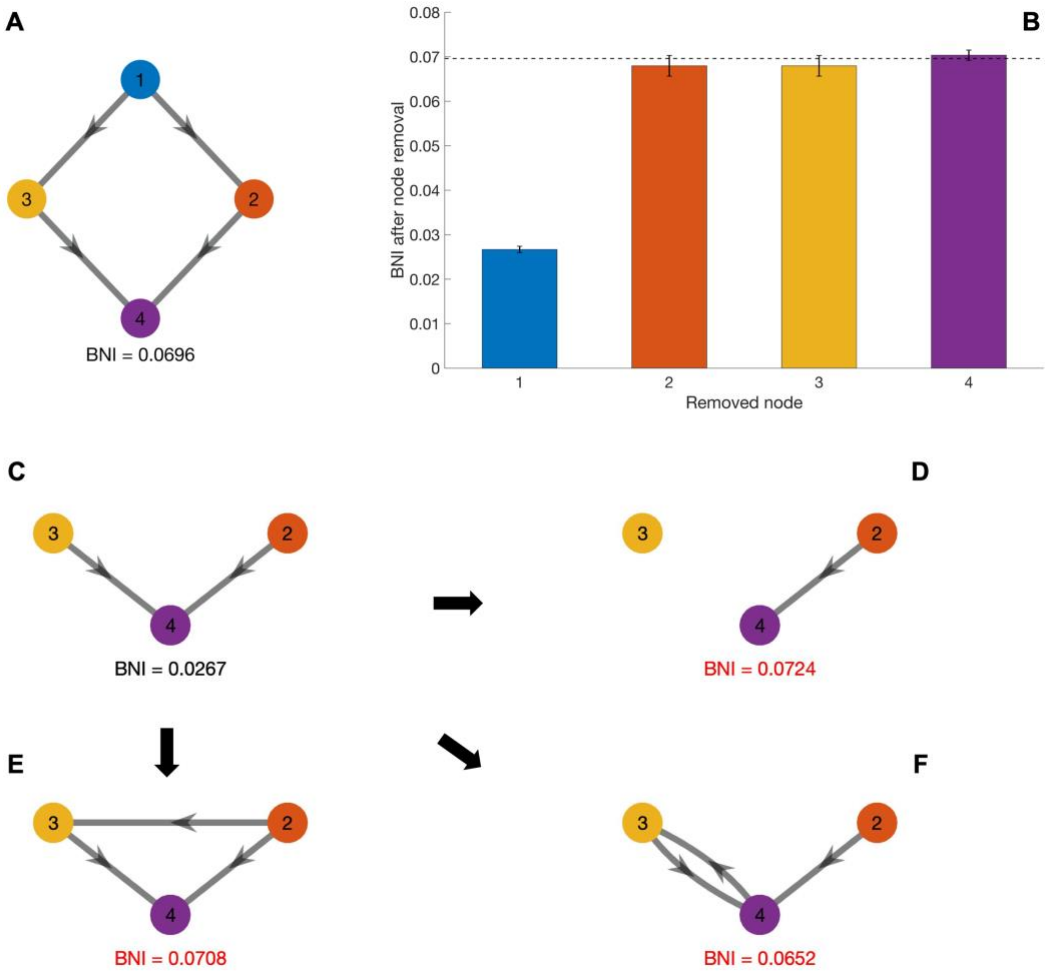

Fig. 6: (A) Exemplar network with 4 nodes. (B) *BNI* for the resulting networks after the removal of each of the 4 nodes individually (dashed line represents *BNI* before node removal). (C) Resulting network after the removal of node 1 (node removal that leads to the lowest *BNI*). (D, E and F) Resulting networks after removing or adding one edge in the network in (C), evidencing a clear increase in the *BNI*.

D. Evaluation of lager networks

This effect is not an artefact resulting from small network sizes. In Fig. 7 we find similar effects in a network of 10 nodes: a size more in line with the typical network sizes obtained from scalp, stereo or intracranial EEG[42]. The network presented in Fig. 7(A) has a relatively high *BNI*. The effects of removing all nodes individually are presented in Fig. 7(B), and it suggests that only the removal of node 1 leads to a significant reduction in the *BNI*. The network resulting from removing node 1 is presented in Fig. 7(C). This network is formed by two cycles, one involving nodes 2, 3, 4, 5 and 10, and the other by nodes 6, 7, 8, and 9. The cycles are connected by an edge between nodes 9 and 10. This network presents a relatively low *BNI*. However, if we probe the *BNI* stability by adding or removing individual edges, Fig. 7(D) shows that for over 10% of the resulting networks the *BNI* increases significantly, sometimes to values even higher than before the removal of node 1.

These findings are a potentially important consideration for pre-surgical planning. A strategy that a priori leads to a substantial reduction in *BNI* can result in a remaining network that is prone to a return to high seizure propensity with only a few connections added or removed.

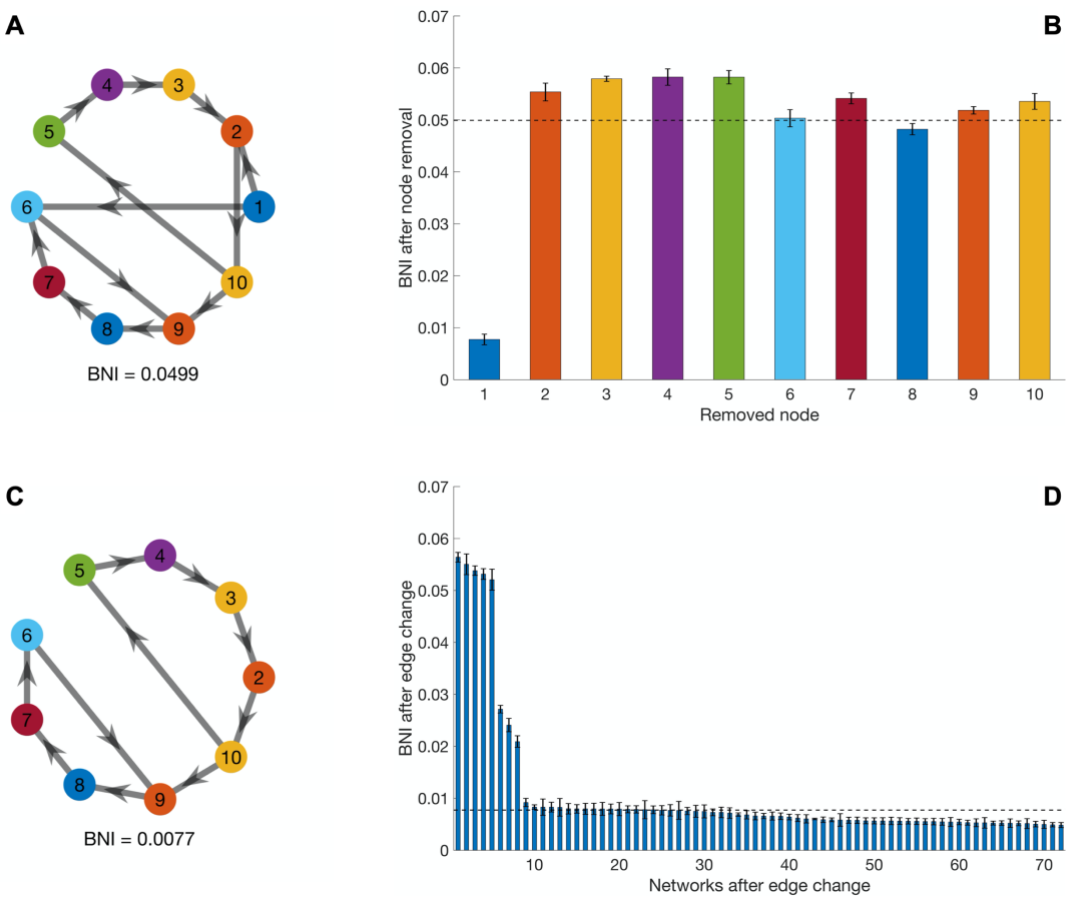

Fig. 7: (A) Exemplar network with 10 nodes. (B) *BNI* for the resulting networks after the removal of each of the 10 nodes individually (dashed line represents *BNI* before node removal). (C) Resulting network after the removal of node 1 (node removal that leads to the lowest *BNI*). (D) *BNI* for all 72 possible networks obtained by removing or adding one edge in the network in (C), sorted by decreasing *BNI* (dashed line represents *BNI* before edge change). Note that 8 networks (>10%) present a significant increase in the *BNI*.

IV. Discussion

In this paper we used a canonical dynamic network model to explore seizure propensity in brain networks. We showed that due to the interplay of coupling between brain regions and the excitability within brain regions, a decrease in *BNI* is correlated with an increased number of edges within the network. We further showed that the hierarchy of the network plays a crucial role in the level of *BNI*: the presence of a single driving node leads to high values of *BNI*, competing driver nodes typically result in intermediate levels of ictogenicity, whilst strongly connected networks tend to present very low ictogenicity.

Building on these observations, we systematically evaluated how removal of network nodes influences the ictogenicity of the remaining network. These so-called virtual resections are effectively an *in silico* proxy for brain surgery, enabling the relative merits of alternative surgical strategies to be evaluated. Of particular importance is the robustness of an intervention to future evolution of the remaining network. To investigate this, we systematically studied the impact on *BNI* of adding or removing edges within a network for which a node had been previously removed. We found networks for which initially high *BNI* was significantly reduced upon removal of a specific node. However, any alterations to the remaining network led to a return to high levels of *BNI*, similar to those prior to node removal.

A potential limitation of our study is that *BNI* is agnostic to seizure-frequency: a simulation in which all nodes enter the seizure-like state for 20 seconds has the same *BNI* as a simulation in which all nodes enter the seizure-like state ten times for 2 seconds each. In addition, identical values of *BNI* can be achieved through different mechanisms and patterns of activity. However, in contexts where the differentiation between specific seizure patterns are important, the *BNI* framework described in this work can be extended. For example, Lopes *et al.*[39] have used the average slope of the *BNI* as a function of the coupling strength (what the authors called the *Ictogenic Spread*) to classify genetic generalized epilepsy versus mesial temporal lobe epilepsy. Woldman *et al.*[43] introduced two measures: the onset index and the participation index that incorporate the level of synchronised activity within brain regions and the ability of those brain regions to either drive seizure onset, or to become involved in such activity. Furthermore, these potential limitations are likely to be context dependent. For example, people with epilepsy may place high value on measuring the number of seizures they experience, whilst the total duration of those events is less important. On the other hand, a neurosurgeon planning surgery, will primarily be concerned with how a specific resection will affect a given, baseline, seizure propensity. We finally note that the results of our work are not impacted by these limitations, since we are interested in seizure susceptibility more generally, independent of any specific activity patterns.

Taking into account the robustness of a perturbed network to subsequent alterations to its connectivity is an important consideration in pre-surgical planning. For example, there may be competing strategies which result in an initial reduction in seizure propensity. However, one is more sensitive to subsequent network alterations than the other. Therefore, an important next step for this research is the application of these theoretical concepts to networks inferred directly from clinical data. This would provide the opportunity to better characterise long-term seizure freedom, given an apparently successful surgical intervention.

Acknowledgments
LJ and JRT acknowledge financial support from the EPSRC via grant EP/N014391/1. LJ, WW and JRT acknowledge financial support from Innovate UK via grant TS/R00546X/1. WW acknowledges financial support from the MRC (MR/N01524X/1) and from Epilepsy Research UK (F2002). WW and JRT are co-founders of Neuronostics.

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. WHO | Epilepsy. *WHO* (2017).
2. Banerjee, P. N., Filippi, D. & Allen Hauser, W. The descriptive epidemiology of epilepsy-A review. *Epilepsy Research* (2009).
3. Kwan, P. & Brodie, M. J. Early identification of refractory epilepsy. *N. Engl. J. Med.* (2000).
4. Fisher, R., Salanova, V., Witt, T., Worth, R., Henry, T., Gross, R., Oommen, K., Osorio, I., Nazzaro, J., Labar, D., Kaplitt, M., Sperling, M., Sandok, E., Neal, J., Handforth, A., Stern, J., DeSalles, A., Chung, S., Shetter, A., *et al.* Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. *Epilepsia* (2010).
5. Duncan, J. S., Winston, G. P., Koepp, M. J. & Ourselin, S. Brain imaging in the assessment for epilepsy surgery. *Lancet Neurol.* **15**, 420–433 (2016).
6. De Tisi, J., Bell, G. S., Peacock, J. L., McEvoy, A. W., Harkness, W. F., Sander, J. W. & Duncan, J. S. The long-term outcome of adult epilepsy surgery, patterns of seizure remission,

and relapse: A cohort study. *Lancet* **378**, 1388–1395 (2011).
7. Mohan, M., Keller, S., Nicolson, A., Biswas, S., Smith, D., Farah, J. O., Eldridge, P. & Wieshmann, U. The long-term outcomes of epilepsy surgery. *PLoS One* (2018).
8. Sheikh, S. R., Kattan, M. W., Steinmetz, M., Singer, M. E., Udeh, B. L. & Jehi, L. Cost effectiveness of surgery for drug resistant temporal lobe epilepsy in the US. *Neurology* (2020).
9. Engel, J. Surgery for Seizures. *N. Engl. J. Med.* (1996).
10. Engel, J. J. The current place of epilepsy surgery. *Curr. Opin. Neurol.* (2017).
11. Kramer, M. A. & Cash, S. S. Epilepsy as a Disorder of Cortical Network Organization. *Neurosci.* **18**, 360–372 (2012).
12. Richardson, M. P. Large scale brain models of epilepsy: dynamics meets connectomics. *J. Neurol. Neurosurg. Psychiatry* **83**, 1238–1248 (2012).
13. Van Diessen, E., Diederen, S. J. H., Braun, K. P. J., Jansen, F. E. & Stam, C. J. Functional and structural brain networks in epilepsy: What have we learned? *Epilepsia* (2013).
14. Geier, C. & Lehnertz, K. Long-term variability of importance of brain regions in evolving epileptic brain networks. *Chaos* (2017).
15. Li Hegner, Y., Marquetand, J., Elshahabi, A., Klamer, S., Lerche, H., Braun, C. & Focke, N. K. Increased Functional MEG Connectivity as a Hallmark of MRI-Negative Focal and Generalized Epilepsy. *Brain Topogr.* (2018).
16. van Mierlo, P., Höller, Y., Focke, N. K. & Vulliemoz, S. Network Perspectives on Epilepsy Using EEG/MEG Source Connectivity . *Frontiers in Neurology* vol. 10 721 (2019).
17. Fisher, R. S., Cross, J. H., French, J. A., Higurashi, N., Hirsch, E., Jansen, F. E., Lagae, L., Moshé, S. L., Peltola, J., Roulet Perez, E., Scheffer, I. E. & Zuberi, S. M. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. *Epilepsia* (2017).
18. Stam, C. J. Modern network science of neurological disorders. *Nature Reviews Neuroscience* (2014).
19. Woldman, W. & Terry, J. R. Multilevel Computational Modelling in Epilepsy: Classical Studies and Recent Advances. in *Validating Neuro-Computational Models of Neurological and Psychiatric Disorders* (eds. Bhattacharya, B. S. & Chowdhury, F. N.) 161–188 (2015).
20. Terry, J. R., Benjamin, O. & Richardson, M. P. Seizure generation: The role of nodes and networks. *Epilepsia* **53**, (2012).
21. Kalitzin, S. N., Velis, D. N. & Lopes da Silva, F. H. Stimulation-based anticipation and control of state transitions in the epileptic brain. *Epilepsy Behav.* (2010).
22. Benjamin, O., Fitzgerald, T. H., Ashwin, P., Tsaneva-Atanasova, K., Chowdhury, F., Richardson, M. P. & Terry, J. R. A phenomenological model of seizure initiation suggests network structure may explain seizure frequency in idiopathic generalised epilepsy. *J. Math. Neurosci.* **2**, 1 (2012).
23. Milton, J. & Jung, P. *Epilepsy as a Dynamic Disease*. (Springer Berlin Heidelberg, 2003).
24. Moraes, M. F. D., de Castro Medeiros, D., Mourao, F. A. G., Cancado, S. A. V. & Cota, V. R. Epilepsy as a dynamical system, a most needed paradigm shift in epileptology. *Epilepsy and Behavior* (2019).
25. Hutchings, F., Han, C. E., Keller, S. S., Weber, B., Taylor, P. N. & Kaiser, M. Predicting Surgery Targets in Temporal Lobe Epilepsy through Structural Connectome Based Simulations. *PLoS Comput. Biol.* (2015).
26. Goodfellow, M., Rummel, C., Abela, E., Richardson, M. P., Schindler, K. & Terry, J. R. Estimation of brain network ictogenicity predicts outcome from epilepsy surgery. *Sci. Rep.* **6**, 29215 (2016).
27. Sinha, N., Dauwels, J., Kaiser, M., Cash, S. S., Westover, M. B., Wang, Y. & Taylor, P. N. Predicting neurosurgical outcomes in focal epilepsy patients using computational modelling. *Brain* **140**, 319–332 (2016).

28. Khambhati, A. N., Davis, K. A., Lucas, T. H., Litt, B. & Bassett, D. S. Virtual Cortical Resection Reveals Push-Pull Network Control Preceding Seizure Evolution. *Neuron* (2016).
29. Jirsa, V. K., Proix, T., Perdikis, D., Woodman, M. M., Wang, H., Bernard, C., Bénar, C., Chauvel, P., Bartolomei, F., Bartolomei, F., Guye, M., Gonzalez-Martinez, J. & Chauvel, P. The Virtual Epileptic Patient: Individualized whole-brain models of epilepsy spread. *Neuroimage* **145**, 377–388 (2017).
30. Lopes, M. A., Richardson, M. P., Abela, E., Rummel, C., Schindler, K., Goodfellow, M. & Terry, J. R. An optimal strategy for epilepsy surgery: Disruption of the rich-club? *PLoS Comput. Biol.* (2017).
31. Johnston, M. V. Clinical disorders of brain plasticity. *Brain and Development* (2004).
32. Junges, L., Lopes, M. A., Terry, J. R. & Goodfellow, M. The role that choice of model plays in predictions for epilepsy surgery. *Sci. Rep.* **9**, 7351 (2019).
33. Hebbink, J., Meijer, H., Huiskamp, G., van Gils, S. & Leijten, F. Phenomenological network models: Lessons for epilepsy surgery. *Epilepsia* **58**, e147–e151 (2017).
34. Neiman, A. Synchronizationlike phenomena in coupled stochastic bistable systems. *Phys. Rev. E* (1994).
35. MacKay, R. S. & Sepulchre, J. A. Multistability in networks of weakly coupled bistable units. *Phys. D Nonlinear Phenom.* (1995).
36. Ashwin, P., Creaser, J. & Tsaneva-Atanasova, K. Fast and slow domino regimes in transient network dynamics. *Phys. Rev. E* (2017).
37. Petkov, G., Goodfellow, M., Richardson, M. P. & Terry, J. R. A critical role for network structure in seizure onset: A computational modeling approach. *Front. Neurol.* **5**, (2014).
38. Lopes, M. A., Junges, L., Woldman, W., Goodfellow, M. & Terry, J. R. The Role of Excitability and Network Structure in the Emergence of Focal and Generalized Seizures. *Front. Neurol.* (2020).
39. Lopes, M. A., Perani, S., Yaakub, S. N., Richardson, M. P., Goodfellow, M. & Terry, J. R. Revealing epilepsy type using a computational analysis of interictal EEG. *Sci. Rep.* (2019).
40. Lopes, M. A., Junges, L., Tait, L., Terry, J. R., Abela, E., Richardson, M. P. & Goodfellow, M. Computational modelling in source space from scalp EEG to inform presurgical evaluation of epilepsy. *Clin. Neurophysiol.* (2020).
41. Rosenow, F. & Lüders, H. Presurgical evaluation of epilepsy. *Brain* **124**, 1683–1700 (2001).
42. Aminoff, M. J. *Aminoff's Electrodiagnosis in Clinical Neurology*. *Aminoff's Electrodiagnosis in Clinical Neurology* (2012).
43. Woldman, W., Schmidt, H., Abela, E., Chowdhury, F. A., Pawley, A. D., Jewell, S., Richardson, M. P. & Terry, J. R. Dynamic network properties of the interictal brain determine whether seizures appear focal or generalised. *Sci. Rep.* **10**, 7043 (2020).