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**Highlights** (3-5 bullet points as highlights, each highlight should be 85 characters or less)

- Debates on the network theory of epilepsy
- What is an epileptic network?
- How can we control an epileptic network?

**Abstract**

Debates on six controversial topics on the network theory of epilepsy were held during two debate sessions, as part of the International Conference for Technology and Analysis of Seizures, 2019 (ICTALS 2019) convened at the University of Exeter, UK, September 2-5 2019.

The debate topics were (1) From pathologic to physiologic: is the epileptic network part of an existing large-scale brain network? (2) Are micro scale recordings pertinent for defining the epileptic network? (3) From seconds to years: do we need all temporal scales to define an epileptic network? (4) Is it necessary to fully define the epileptic network to control it? (5) Is controlling seizures sufficient to control the epileptic network? (6) Does the epileptic network want to be controlled? This article, written by the organizing committee for the debate sessions and the debaters, summarizes the arguments presented during the debates on these six topics.

Keywords: Epileptic network
Ictogenesis
Epileptogenesis
Seizure control
Nodes
Edges

## 1. Introduction

Based on earlier works by Brazier, Penfield, Jasper, and others in the 1940's to 1970's [1, 2] and clinical observations a network theory of epilepsy was proposed more than 15 years ago [3]. There have been considerable advances made on network studies in epilepsy [4] and in neuroscience in general [5] since that time. While progress has indubitably been made on the use of network measures to understand epilepsy, important aspects of the network theory of epilepsy remain poorly defined. Our ability to place this theory on firmer ground depends to some extent on our ability to clearly define existing controversies on the network theory of epilepsy and seek to clarify and address them.

The International Conference for Technology and Analysis of Seizures, 2019 (ICTALS 2019) was convened at the University of Exeter, UK, September 2-5 2019. This conference brought together investigators from diverse technical and scientific backgrounds to, among other goals, assess the state of seizure prediction and seizure control and to identify impediments to progress in these important areas. Three members of the Scientific Advisory Board for ICTALS 2019 (K.L., B.S., and H.P.Z.) convened two debate sessions on the network theory of epilepsy during the conference. Through discussion the following two general areas and six controversial questions on the network theory of epilepsy were preselected. In Session I we sought to define an epileptic network, by asking if it was an existing network or a novel network formed during epileptogenesis and clarifying the spatial and temporal definitions of the network. In Session II

we posed questions on the very open area of how to control an epileptic network. The debate topics in Session II addressed if it was necessary to fully define the network in order to control it, if controlling seizures, a symptom expressed by the network, would suffice to control the network and most fundamentally would the network want to be controlled.

Debaters who were considered to be able to do justice to the defined questions were pre-selected. These debates were not designed to resolve the selected topics, and no winner was selected. The format was designed primarily to highlight an open topic and clarify opposing perspectives. In fact, not all of the debaters even fully supported the positions which they were asked to argue. The debate sessions, debates, and this manuscript follow a previously successful similar effort from the Fourth International Workshop on Seizure Prediction (IWSP4) [6]. The ICTALS meetings are part of the same workshop series as the IWSP series.

Each debate was conducted over 30 minutes. For each debate, the debater listed first spoke first for the affirmative position and this was followed by a presentation of the opposing position. The debaters were each allowed 6 minutes to present evidence to support their position. This exchange was followed by brief comments by a discussant for up to 3 minutes followed in turn by a 15-minute open forum for audience participation. Many of the arguments presented by the debaters were taken from the literature, although some included new or previously unpublished work. This article seeks to concisely summarize the arguments and counterarguments which were presented on each of the debate topics.

## 2. Debate 1: From pathologic to physiologic: is the epileptic network part of an existing large-scale brain network?

### *2.1 Hitten Zaveri, Position: Yes*

In the network theory of epilepsy, epileptogenesis is the process by which an epileptic network is formed. The question posed here is, is this an existing network, that is a normal network hijacked during epileptogenesis, or a novel network which is formed during epileptogenesis? The challenge to answering this question lies in the gaps in our knowledge because we remain at an early stage in the development of the network theory of epilepsy and because we lack definitive information on normal networks in humans [7, 8]. Because of these limitations the argument posited here is based on studies of epileptogenesis in non-human primate [9, 10] and

rodent [11-13] models of epilepsy, and an observed overlap between the epileptic network and known networks in humans [7].

First, studies by Cleeren and co-workers conducted in two monkeys over approximately 16 months are instructive [9, 10]. The animals underwent electrical kindling of the amygdala with multiple ictal perfusion SPECT evaluations and an electrical microstimulation with fMRI (EM-fMRI) study of the fully kindled animals. A slow but progressive emergence of distinct large scale networks through epileptogenesis was observed with both overlap and distinction between ictal perfusion and EM-fMRI activations [9, 10]. Differences observed between the two animals were ascribed to small differences in the placement of the stimulating electrode resulting in recruitment of different networks in the two animals.

Second, diffusion tensor imaging (DTI) [14], c-Fos immunohistochemistry [15], electrophysiology and neurochemistry [16] studies of epileptogenesis in a rodent model of medial temporal lobe epilepsy (MTLE) [11-13] also reveal epileptogenesis to be a progressive process which unfolds over days and weeks [17]. More subclinical and milder seizures were observed early and severe seizures were observed later in epileptogenesis [17]. Concomitant with the increasing severity increasingly greater regions of the brain were more efficiently involved in the seizures [16]. The regions involved in epileptogenesis were by and large those which may be expected in MTLE.

Third, there is an intriguing emerging overlap between normal networks and epilepsy. First, there is evidence that population activity expressed during seizures is replayed during rest or sleep periods, suggesting an overlap between the epileptic network and processes for long-term memory consolidation [18]. Second, there is evidence that epilepsy and mood disorders have overlapping functional and cognitive networks, suggesting a possible relationship of the epileptic network and networks such as the default mode, dorsal attention, ventral attention, executive control, and reward-emotion networks [7].

In summary, SPECT (ictal, perfusion), EM-fMRI (interictal, EM-fMRI activations), c-Fos (ictal, neuronal activation), electrophysiology (ictal, propagation), DTI (interictal, structural connectivity) studies of epileptogenesis implicate widespread network changes which occur early with increasingly more efficient involvement of progressively larger neuronal populations. Though there is variability between animals the suggestion is that the emerging epileptic network leverages connectivity between known and expected cortical and sub-cortical

structures. Second, there is evidence of an overlap between normal networks and the epileptic network in humans. Based on these observations we argue that the epileptic network is part of an existing brain network and is not a novel network.

*2.2 Catherine Schevon, Position: No*

Epileptic networks, to date, have been largely a notional concept based on clinical observations from the evaluation of epilepsy surgery patients with intractable focal syndromes [3]. In order to address the major question of this debate, it is necessary to ground this concept in neurophysiological principles, by considering the key cellular components whose interactions result in the manifestation of observable network behavior.

Functional connectivity is determined by measuring the correlation of biological signals from EEG or fMRI studies during a fixed time interval between two pre-defined recording sites or regions of interest. It is expected that functional connectivity should be constrained by, and correlate with, anatomical connections [19]. Indeed, seizure propagation pathways have been shown to correspond to those of normal activity in an acute rodent picrotoxin seizure model [20] – implying that the connectivity components utilized by epileptic networks are not novel. However in chronic epilepsy models, novel small-scale structural pathways have been directly demonstrated, and shown to underpin seizure initiation and propagation. These include pathologically recurrent excitatory connections [21] and mossy fiber sprouting in the dentate gyrus [22]. The role of large-scale structural network reorganization is less clear. While large-scale structural aberrations are common in epilepsy surgery patients, many patients exhibit no detectable structural brain abnormalities [23].

If that is so, then how might large-scale, novel functional connectivity arise in the absence of strong structural interconnections? We must first consider whether our existing methods of inferring the epileptic network provide an accurate assessment of long-range neural communication. EEG is composed primarily of summated postsynaptic potentials, and is typically blind to action potentials. That is, strong cross-site EEG correlation does not necessarily imply coordinated neural firing across sites. Instead, the pattern of neural firing at a given recording location during a seizure is shaped by the balance of excitation and inhibition at that location. In support of this hypothesis, striking differences in neuronal activity have been

demonstrated underlying similar low-frequency ictal rhythms across recording locations in both human and animal studies [24, 25].

A possible explanation for novel functional connectivity is that it may arise in the setting of localized impairment of inhibition. Aberrant GABAergic function has been shown to be a factor independent of connectivity in potentiating seizure propagation [26, 27]. In this scenario, strong excitatory barrages generated by an ongoing seizure are typically masked by inhibition, but can be unmasked if inhibition is impaired at a distant site [26]. Although feedforward inhibition has generally been studied as a short-range, microscale phenomenon [28], inhibition can also have long-range effects [29] and may be integral in shaping seizure evolution and termination. As little is known about the long-distance interplay of excitatory and inhibitory activity in the setting of epileptiform activity, more research is needed in order to further our understanding of the physiology of large-scale epileptic networks.

## 3. Debate 2: Are micro scale recordings pertinent for defining the epileptic network?

### *3.1 Premysl Jiruska, Position: Yes*

In the last two decades, epileptology has seen wider introduction of micro-electrode recording in humans [30]. In the past, few studies used this technology to gain insight into the neuronal dynamics within epileptic foci between and during the seizures, but with advances in technology, various new types of electrodes were developed ranging from micro-electrode arrays to hybrid electrodes [24, 31, 32]. The recent studies from micro-electrodes brought unprecedented information about the functional organization of epileptic networks at micro-, meso- to macro- scales and described the epileptic activity of single neurons (pyramidal cells and interneurons) simultaneously with the activity at small and large neuronal population level. Micro-electrode recordings identified the existence of various phenomena like micro-discharges [33], high-frequency oscillations (HFOs) [34] or micro-seizures [35]. The probability of recording these forms of epileptiform activity is lower when using standard macro-electrodes. The information from micro-electrodes is informative about the functional organization of the epileptic tissue into the multiple independent pathological neuronal clusters capable of generating these forms of epileptiform activities [34]. During seizures, the neuronal clusters merge together and generate epileptic activity in synchrony which can be detected using macro-electrodes as a macro-seizure or interictal epileptiform discharges [35]. The study of seizure propagation using

micro-electrodes revealed that active generation of epileptic activity manifests as the presence of fast gamma activity in the seizure onset zone and which then spreads with the seizure propagating wavefront reflecting the erosion of inhibitory surround [33]. The ability to identify the fast gamma activity and precisely localize the seizure onset zone seemed to be a predictor of good outcome of surgical treatment of epilepsy.

The micro-electrode recording played a key role in research on HFOs in humans. HFOs are considered as a marker of epileptogenic tissue and seizure onset zone. Here, the micro-electrode approaches contributed to the description of the role of individual neuronal subtypes in HFO genesis in humans [34]. Moreover, micro-electrodes displayed higher sensitivity to detect HFOs and it is assumed that the utilization of micro-electrode recordings can increase the probability of HFO detection, improve the delineation of epileptogenic tissue and lead to improved surgical outcome [31]. Recent studies also demonstrated the existence of epileptic activities with a frequency above 600 Hz which are called very-high HFOs. Their spatial distribution also correlates with epileptogenic tissues [36]. It was proposed that their location can be highly informative during the planning of surgical resection.

*3.2 John G. R. Jefferys, Position: No*

It is speculative, how much the introduction of micro-electrode recording will improve the traditional approach to presurgical diagnosis. It seems that currently used approaches of recording intracranial activity with macro-electrodes are sufficient to provide clinically reliable information about the spatiotemporal properties of the most relevant epileptiform phenomena, i.e. interictal discharges, HFOs and seizures. For example, the majority of studies that explored the clinical utilization of HFOs in presurgical diagnosis was based on macro-electrode recordings [37]. Another advantage is that macro-electrodes cover large brain areas and provide information on much larger spatial scales which seems clinically more important than information on micro-scale because the epileptic network can be often very spatially extensive. Similar approaches using micro-electrodes would require hundreds or thousands of micro-contacts, and positioning them could cause more damage than macro-electrodes where lower spatial selectivity can reduce the number of implanted probes. To date, it seems that micro-electrode recordings are not crucial for epilepsy surgery. Presurgical examination would rather benefit from the improved and more detailed spatial sampling with macro-electrodes to

simultaneously cover larger brain areas at the surface or depth of the sulci and in deep brain structures.

Micro-electrode recordings have substantially contributed to the understanding of physiological brain functions, the elucidation of pathophysiological principles of epilepsy in humans, and have made considerable contributions to understanding the normal operation of neuronal networks. Currently, the micro-electrode recording is not necessary for presurgical examination but we can expect, that in the near future, the utilization of micro-electrodes techniques in humans will continue to grow dramatically. We will observe advances especially in the field of brain-machine interface research where information about the activity from small neuronal populations or single neurons is critical. The growth of micro-electrode utilization will be spurred by new types of electrodes that are being developed like injectable [38] or dissolvable electrodes [39]. In epileptology, wider application of micro-electrode recording will depend on two main factors. Firstly, it is important to understand the functional significance of micro-scale epileptiform activity in ictogenesis, epileptogenesis or disease activity. The research will need to determine whether these forms of epileptiform activity provide any additive (or even superior) clinical information beyond macro-electrode recording. The second crucial step represents the development of new tools for signal analysis. The visual review of long-term recordings from hundreds or thousands of micro-channels is virtually impossible. Therefore, the introduction of micro-electrodes recording will be dependent on the availability of signal processing tools that can provide reliable quantitative information which can be easily interpreted by clinicians to guide their decisions about the resection extent. We predict the future evolution of recording of electrical brain activity in epilepsy will go in two opposing directions. One direction will go towards fine micro-recordings which can be used also for precise neurostimulation to control the activity of small neuronal populations. The other direction will be towards improving the existing macro-recordings by increasing their information yield using advanced techniques of signal processing and especially towards improving the non-invasive scalp recording. Which direction will be the more important in treating epilepsy remains to be determined.

## 4. Debate 3: From seconds to years: do we need all temporal scales to define an epileptic network?

*4.1 Gregory Worrell, Position: Yes*

The networks underlying the generation of epileptic seizures are organized on spatial scales spanning cells (neurons and glia), ensembles of cells, to interacting cortical, subcortical, and brainstem systems. These diverse networks support critical physiological functions (e.g. memory, movement and language, sleep-wake behavioral states) and the pathological expression of seizures. These neuronal networks operate across time-scales ranging from the millisecond dynamics of neurons and ensembles and their excitability is modulated by various systems acting over minutes, days, and months.

The study of biological rhythms [40] or chronobiology, describes ultradian cycles with periods less than a day (< 24 hrs), circadian cycles of a day (~24 hrs), and infradian cycles with periods longer than a day (> 24 hrs). For example, fluctuations in cortical excitability occur during the day manifesting in changes in alertness, during the sleep-wake cycle, and with monthly menstrual cycles in females. Investigations of focal epilepsy in humans and animals show the temporal dynamics of seizure generation occur across the time scales of cellular networks in single neuron and ensemble activity [41-43] and local field potentials [44, 45]. The modulation of these epileptic ensembles by sleep and wake cycles may even be important for consolidation of epileptic seizures engrams [18, 46]. Furthermore, cortical excitability and seizure generation is modulated by time scales spanning days, weeks, and months [47, 48].

Thus, tracking the complex spatiotemporal dynamics of the electrical activity of the brain networks underlying human epilepsy requires large-scale electrophysiology recordings spanning cortical, subcortical and brainstem systems over milliseconds to months (~$10^{-3}$ to $10^{6}$ seconds). It is widely recognized that the unpredictability of seizures is one of the most, if not the most, disabling aspects of epilepsy for people. The uncertainty also dictates the use of daily medications that can produce side effects, and in ~1/3 people does not eliminate all seizures. The possibility of a seizure warning system based on brain excitability, i.e. seizure probability, would allow intelligent therapy based on seizure risk chronotherapy [49] and brain state dependent therapy [50].

*4.2 Andreas Schulze-Bonhage, Position: No*

Recent results demonstrating long-term fluctuations in seizure proneness and neuronal activation patterns early during seizures may suggest that a wide range of dynamics are relevant to characterize the epilepsy-related brain properties. Defining the epileptic network, in

contrast, means to identify a particular core structural and functional network with particular outlasting pro-epileptic dynamics.

Not all spatial scales are needed to define this network.

1. as it is technically **not feasible**
2. as it is **not necessary**
3. as it may even be **inadequate**

1. To separate out an identified epileptic network, its characterization by spatial coverage of multiple nodes involved or not involved in the seizure generating network is needed. Even with gross undersampling using high temporal assessment over periods of weeks to months at high sampling rate will lead to amounts of data which are hard to record, store and analyze. As neither storage nor time series analyses on such amounts of data are usually available at hospitals and research institutions, a selection of appropriate time scales both with regard to temporal resolution and to the duration of the period of analysis is needed to render the application of analytic strategies feasible.

2. There are core properties of an epileptic network which are time-invariant and can be modelled completely without reference to particular time scales. Examples for this are mathematical models of a limited number of nodes and manipulations of the network topology by removing edges which lead to diverse types of emerging focal or extended epileptic patterns [51]. Similarly, many network structures have time-invariant properties, in part related to the underlying structural connectivity, which allows to extrapolate functional topologies from short observation periods [52]. Analyses of physiological networks suggest that it is useful to limit analyses to adequate time periods and temporal resolution. This applies e.g. to fluctuations in the oscillatory binding of brain areas during perceptual tasks [53] and to interactions within memory networks during memory encoding and recall [54].

Furthermore, simultaneous recordings of unit activities and local field potential oscillations at seizure onset show that the relevant information in oscillatory activity is assessable at a temporal resolution of ms, but not in the highly time-resolved activity of individual neurons [55].

Depending on the clinical or scientific question, an appropriate network characterization may involve mostly stable (e.g. structural) or relatively invariant (e.g. functional interictal) connectivity

within the epileptic network. An example is response prediction to vagus nerve stimulation [56] based on electrophysiological assessment limited to a brief period of time in the interictal network state [57]. Probing the network by perturbations may similarly allow to conclude on crucial properties of epileptic networks during short time periods.

Seizure prediction has recently been reported to be improved when analyzing very long-term data and training models over periods of months, to include circadian and ultradian fluctuations in seizure propensity. Thus, the use of long-term time series and compromises in terms of temporal resolution may be useful for particular questions. This application, however, does not serve to identify the epileptic network but rather assesses its modulations caused by fluctuations of dynamics within wider brain networks.

3. Self-organizing properties of networks frequently are not directly reducible to underlying neuronal dynamics as they emerge at mesoscopic spatial and temporal scales. This includes traveling waves, oscillatory behavior and generation of neuronal avalanches, all relevant for the generation of epileptic activity. In particular, critical network dynamics which may be involved in transitions from interictal to ictal dynamics are time-invariant over multiple scales [58]. An assessment at the microsecond level may thus not be adequate, and an assessment at very long-time scales redundant.

In summary, defining a network means to identify the time-invariant, robust and essential structural and functional features. These features can be assessed at proper time scales when using adequate and robust methodological approaches and based on data from restricted time periods. An assessment of fluctuations as microscale and at very long-time scales may rather obscure than clarify the characteristic network properties. Depending on the scientific or clinical question asked, assessing all time scales does not only lead to processing an insurmountable load of data but may not be necessary or even be inadequate to identify the essential features defining the epileptic network.

## 5. Debate 4: Is it necessary to fully define the epileptic network to control it?

### *5.1 Rasesh Joshi, Position: Yes*

Treatment of the epileptic network should simultaneously contain the deleterious effects of seizures and minimize adverse effects on normal brain function. In order to achieve successful control, we argue for the necessity of fully defining the epileptic network across multiple scales.

Our general approach to treating epilepsy has presumed that interfering with a subset of nodes in the *observed* epileptic network is sufficient to disrupt it as a whole. However, the notion of a discrete seizure onset zone (SOZ) being the sole driver of ictogenesis has come into question in recent years [3]. A study of functional networks in intracranial EEG recordings of seizures demonstrated time-varying contributions of nodes that are part of the epileptic network, but outside the SOZ, to the generation and maintenance of seizure [59]. Given the relatively sparse spatial sampling inherent to targeted electrode placement, it is reasonable to think that significant parts of the epileptic network are often omitted in our clinical evaluations [7]. This is somewhat mitigated by extracranial modalities that have wider spatial coverage like scalp EEG and MEG, but these are severely limited in their ability to provide detailed information about deep, subcortical structures involved in seizure. This is of particular importance when considering the prospect of intervening at so-called “choke points” in the network distal from the SOZ (e.g. thalamus) that may prove to have utility in disrupting the entrainment of the network into seizure [60]. We posit that targeting these specific nodes to control the network can only be effective if we contextualize their role in the network as a whole, likely beyond the scope of what we currently observe with any one modality.

We also require a stronger grounding of microscale mechanisms of seizure. Recent work using a model of acute seizure demonstrated reproducible patterns of neuronal recruitment into seizure, with elasticity in time that is dependent on pacing of GABAergic inhibition in the local cellular population [61]. Whether this stereotypy translates into macroscale recordings of spontaneous seizures in the clinical setting remains unclear. Indeed, there may be some discrepancy between the wave-like propagation of some clinical seizures observed in multiunit activity from multielectrode arrays and the seemingly homogeneous, high-amplitude activity recorded in neighboring intracranial EEG electrodes [62]. Furthermore, seizures appear to hijack and repurpose circuitry involved in normal physiological processes of learning and memory, specifically by priming hierarchical oscillatory coupling and through reactivation of neuronal assemblies during sleep [18, 63]. Seizure occurrence also seems to be modulated by rhythms on slow timescales (e.g. infraslow, circadian, multidien) [48, 64-66].

The broader implication of these findings and many others is that the epileptic network evolves dynamically in time and across multiple spatial scales, though we often treat it as static. This also perhaps raises question of whether we can confidently say that our attempts at invasive intervention without full characterization of the network are truly successful. Epilepsy therapeutics should ultimately be targeted at ameliorating the underlying network pathology as a whole, not just the signals produced by it.

*5.2 Björn Schelter, Position: No*

The control of the epileptic network is one of the holy grails in medicine promising to open new routes to successfully treat at least the symptoms of this devastating disease. But is it the entire network that we need to fully define in order to be able to control it?

From a purely pragmatic standpoint, it is seizure freedom that is the goal of a first line treatment of epilepsy, through strictly speaking it is the treatment of symptoms. Anti-epileptic drugs [67] or resective surgery [68] are only two treatment options successfully applied to date, not seldomly leading to seizure freedom. It is beyond doubt that neither approach relies on a complete definition of the network, though both effectively control the most impairing symptoms, the seizures. While anti-epileptic drugs target various processes in the brain to prevent seizures, surgical removal of the focus targets one specific part of the epileptic network. There is increasing evidence that the focus is not even a distinguished part of the epileptic network quantified by typical network measures, such as betweenness centrality, etc [69].

The natural question therefore arises if better treatment strategies or less invasive ones would be available if we were to better or fully define the epileptic network. There is increasing evidence that epileptogenesis as well as the ictogenesis are processes involving large parts if not the entire brain network [3]; it is still undecided whether there is a separate epileptic network or whether the brain network as a whole becomes epileptic in the process of epileptogenesis. In other words, asking to fully define the epileptic network might well require the complete specification of the brain as a network. There are indeed large consortia like the blue brain project aiming to achieve a better understanding and characterisation of the brain, including its understanding as a network. However, it is probably not the anatomical but the functional network that we need to define [70]. Assuming this task can be completed it is certainly a “long and winding road.” If we assume for now that it will be possible to fully define the brain

functional network, will this automatically result in a better controllability of the network? While this might be the case, there is definitely an argument to be made that having access to the full definition of the epileptic/brain network will come with an over-specified and over-complicated pool of information that will ultimately hinder the successful control of the seizures and is indeed not needed [71].

A better understanding of the epileptic network will certainly be helpful but requiring a complete specification goes too far in my opinion. This also ensures that vital research towards controlling seizures continues and is not put on hold until such time that we have a complete specification of the brain network. There are obvious parallels to the sequencing of the human genome which presented a milestone when it became possible, but this vast amount of information has not resulted in the treatment of all diseases though the complete set of information is essentially available for everybody.

## 6. Debate 5: Is controlling seizures sufficient to control the epileptic network?

### *6.1 Viktor Jirsa, Position: Yes*

If we were able to control seizures, would we be able to control the epileptic network? The answer is likely to be yes, at least to a large degree. A seizure is a dynamic event of abnormal oscillatory neural activity defined by a beginning (onset), an end (offset), and a period in-between (epoch of evolution of spatiotemporal activity within the network in between the two transitions). As a seizure separates brain activity into epochs of ictal and non-ictal activity, understanding seizure control demands both, control of the epileptic network during the ictal and non-ictal epochs, all from the perspective of the trinity of onset, offset, and evolution.

Onset/Offset: A deep understanding of seizure onsets/offsets is obligatory to provide targets for control. Such understanding can be obtained by detailed modeling of the physiological mechanisms, or alternatively phenomenological modeling of the emergent dynamics. The former is essentially impossible in the human due to high dimensionality and degeneracy of variables [72]. The latter approaches allow classifications of seizures in terms of their dynamics, more precisely in terms of their pairing of onset and offset transition types, so-called bifurcations [73]. Each seizure class is generic and shows highly characteristic behaviors at the onset/offset transitions such as frequency and amplitude scaling or multistability [74]. The seizure class will

determine, for instance, if a seizure is susceptible to be terminated via focal stimulation. This may comprise methods to force the system out of the oscillatory state if the non-ictal state co-exists (depending on the seizure type) or phase-averaging techniques, essentially destroying the coherence of the oscillation of the cells in the epileptogenic zone.

Evolution: During the ictal period, between onset and offset, the seizure evolves in space and time. The transitions into and out of the ictal states are dominated by temporal features (bifurcations), which ensues a treatment in terms of dynamics for control, whereas the spatiotemporal evolution of the epileptic network demands a network perspective. As a consequence, seizure relief can be achieved in some cases by stopping the seizure propagation, even though the full seizure is not being controlled. Promising approaches in seizure control are currently network modulation via minimally invasive resection, ablation or stimulation [71, 75, 76]. One or multiple small focal ablations within the EZ have been demonstrated to fully extinguish epileptiform activity. Theoretical studies indicate that such focal ablations can also be applied outside of the EZ, thereby rebalance the network and suppress seizure propagation([71, 76]).

*6.2 Marc Goodfellow, Position: No*

Controlling seizures is a clear aim in the treatment of epilepsy; many of the impairments to quality of life identified by patients are direct or indirect consequences of the recurrence of seizures, for example restrictions on driving, concerns about injury and seizure unpredictability [77]. However, other common detrimental experiences associated with epilepsy such as tiredness, memory problems, depression [78] or other cognitive comorbidities can have a greater impact on quality of life than seizures [79]. It is still unknown to what extent these comorbidities are caused by seizures *per se*, though factors including the existence of impairments before recognition of epilepsy (e.g. [80]), suggest the possibility that they are consequences of underlying abnormalities, rather than consequences of seizures [81].

It is therefore unclear whether treating seizures alone would ameliorate other important symptoms. However, seizure control is often used as a measurement of the success of epilepsy treatment, which includes various options such as AEDs and, if they do not work, surgical intervention. Epilepsy surgery is potentially curative, but long term monitoring has shown that initial seizure freedom can wane over time [68], suggesting that at least in some people, initial

control of seizures has either not “cured” the epileptic network, or has not eliminated the capability of the brain to generate new epileptic networks.

The network paradigm for epilepsy implies that abnormalities in regions of tissue and/or the connections between them leads to the generation of recurrent seizures [82-85]. Recent work has demonstrated that, combined with mathematical models, the network paradigm is useful and has potential practical implications. It has, for example, been validated in the context of predictions for epilepsy surgery [85, 86] and facilitates the development of novel control methods [87]. Most often, mathematical models have focussed on the capability of networks to generate seizures, which gives rise to control strategies based on eliminating seizures or their propagation. However, abnormal dynamics have also been shown to be present in non-seizure (background) states in epilepsy (e.g. [88]). We recently showed in a rodent model that epileptogenesis can be observed in evolving background EEG functional networks [89]. Understanding the mechanisms of altered background EEG dynamics in epilepsy may reveal further information about the disorder and its comorbidities, and may inform the development of new control strategies. For example, rather than using mathematical models to inform the control of seizures, we could seek to control the dynamics of the background state.

In summary, controlling seizures is not sufficient for controlling the epileptic network since it is unclear whether unwanted symptoms would remain unchecked, or whether the epileptic network would in any case begin to produce seizures again at some point in the future. The presence of signatures of epilepsy, its comorbidities and even epileptogenesis in background brain dynamics suggests novel avenues for the control of epileptic networks.

## 7. Debate 6: Does the epileptic network want to be controlled?

### *7.1 Christian Meisel, Position: Yes,*

Yes, brain and epileptic networks want to be controlled in the sense that they have developed adaptation mechanisms that normally keep dynamics in a finely tuned working range. Epileptic networks also want to be controlled in the sense that they do not resist control by antiseizure medication (ASM) in the majority of patients.

Network interactions in cortex want to be carefully controlled in order to prevent premature die-out or runaway excitation when interactions are too weak or too strong. In epilepsy, the importance of tightly controlled network interactions is highlighted by the pathological consequences associated with abnormally high levels of synchronized neuronal activity during seizures. Insights into how brain networks control their interactions to prevent such regimes have come from the study of adaptive networks. Adaptive networks are networks that combine the evolution of the network topology, i.e. the dynamics of the network, with dynamics in the network nodes, i.e. the dynamics on the network [90]. In brain networks the dynamics on the networks can be thought of as the activity of neurons (which is generally constrained by the structural network interactions) while the dynamics of the network include the formation of synapses and dynamical changes in synaptic strengths. It has been shown that simple and purely local plasticity mechanisms are sufficient to robustly self-tune the network as a whole toward an intermediate state that prevents premature die-out on the one side and runaway excitation on the other [91, 92]. Homeostatic synaptic plasticity is one such local synaptic mechanism: it allows neurons to detect changes in their own firing rates to increase or decrease the accumulation of glutamate receptors at synaptic sites and thereby keep their firing range in a certain range [93]. Adaptive networks incorporating homeostatic plasticity are thus a plausible mechanism by which brain networks keep dynamics in a finely tuned regime, a regime that has also been shown to bring about numerous functional and computational benefits [94]. By incorporating these self-controlling mechanisms, brain networks can not only efficiently prevent premature die-out or runaway excitation, but also take advantage of the functional benefits of the intermediate state in between.

It has been suggested that these self-controlling mechanisms based on adaptive networks fail in epilepsy, contributing to the large, non-physiological activity events that define seizures [58]. In this case, networks can be controlled by ASMs. ASMs reduce the risk of runaway excitation by either reduction of excitatory transmission, increase of inhibitory synaptic transmission, or reduction of individual neuron excitability [95]. For the majority of patients ASM treatment is effective and provides good control of seizures. The often-successful reduction of seizures using ASMs that target epileptic networks in the brain is therefore a good indication that these networks at least do not resist control.

Thus, in summary, brain networks in normal conditions want to be controlled in the sense that they have developed inherent mechanisms based on the interplay between dynamics on and of

the network to avoid extreme regimes with premature die-out or runaway excitation. In cases where this fine control fails, networks want to be controlled in the sense that they do not resist control by ASM in the majority of epilepsy patients.

*7.2 Klaus Lehnertz, Position: No*

The human brain is a complex network of interacting nonstationary subsystems, whose complicated spatial-temporal dynamics is still poorly understood. It is a nonlinear, open, dissipative and adaptive system, innately designed to learn. Learning is tightly related to neuronal plasticity [96], which in turn is linked to various disorders of the central nervous system, including epilepsy [97]. In this context, and despite Gowers' aphorism "seizures beget seizures" [98] being a continuing point of contention, one might speculate that seizures present an abnormal learned response to recurrent perturbations – such as seizures [99]. The notion of epilepsy being a "learned" disease may also be supported by observations of psychogenic non-epileptic seizures that manifest after epilepsy surgery, or when epileptic seizures have been controlled by antiepileptic drugs [100, 101].

These considerations, together with drug resistance, limited efficacy of current neuromodulatory therapy, and risk for postoperative seizure relapse [68, 102], suggest an evolving large-scale epileptic network – spanning lobes and hemispheres – to underlie ictogenesis. The network's adaptiveness permits to maintain the learned pathologic functionality. Recent research into the network's local characteristics suggests that ictogenesis is induced by a rearrangement of the network's path structure that is possibly triggered by endogenous and/or exogenous factors and that results in a formation of bottlenecks [69]. Interestingly, earliest indications for such a formation – with lead times up to hours – can be observed in network nodes far from the clinically-defined seizure onset zone, which generate and sustain normal, physiological brain dynamics during inter-ictal periods. Although these network nodes may be considered as targets for neuromodulatory control strategies, efficiently controlling the dynamics of complex networks – such as the epileptic brain – is notoriously difficult [103]. This difficulty may be attributed – among other factors – to stability properties of the evolving large-scale epileptic network with respect to the aforementioned endogenous and/or exogenous factors. Indeed, recent findings indicate that brain stability or brain resilience increases rather than decreases prior to seizures and that the pre-ictal increase clearly exceeds physiologically induced fluctuations of brain resilience [104]. These findings are corroborated by another line of

evidence that suggests a widely assumed model for a loss of resilience prior to a critical transition – such as the pre-ictal phase – and its associated data-driven biomarker – critical slowing down – to be overly simplistic for the human epileptic brain, and unreliable [105].

The aforementioned considerations and research findings suggest ictogenesis in an evolving large-scale epileptic network that efficiently defies control by virtue of its intrinsic plasticity and adaptiveness. Unlearning epilepsy could open new avenues for a more efficient treatment of this complex disease.

## 8. Summary

ICTALS 2019 was the ninth meeting of a series of international scientific congresses held every 18–24 months to bring together the interdisciplinary international seizure prediction group to discuss progress on seizure prediction, seizure generation, and the control of seizures. The debates described here allowed the organizing committee to highlight controversial topics in the network theory of epilepsy that are of relevance to the aims of the workshop and our understanding of epilepsy [4]. The debates allowed a succinct presentation of positions through arguments and counterarguments and an open discussion around these positions. Although the debaters did not necessarily present original results, the debates allowed the debaters to propose arguments from evidence presented in different studies to support their position. A clarification of positions in this manner helps to define where conflicting interpretations on the network theory of epilepsy lie and to clarify opposing perspectives, both of which contribute toward advancement in the field.

## Declaration of Competing Interests

Competing Interests:

1. Dr. Zaveri has a grant award from the NIH (USA) on network analysis for epilepsy surgery, and is named as an inventor on patents for monitoring and modulating human brain activity.

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