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BRIEF COMMUNICATION

Seizure generation: The role of nodes and networks

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Summary

The longstanding dichotomy between the concepts of "focal" and "primary generalized" epilepsy has become increasingly blurred, raising fundamental questions about the nature of ictal onset in localized brain regions versus large-scale brain networks. We hypothesize that whether an EEG discharge appears focal or generalized is driven by the pattern of connections in brain networks, irrespective of the presence of focal brain abnormality. Using a computational model of a simple "brain" consisting of four regions and the connections between them, we explored the effects of altering connectivity structure versus the effects of introducing an "abnormal" brain region, and the interactions between these factors. Computer simulations demonstrated that electroencephalography (EEG) discharges representing either generalized or focal seizures arose purely as a consequence of subtle changes in network structure, without the requirement for any localized pathologic brain region. Furthermore we found that introducing a pathologic region gave rise to focal, secondary generalized, or primary generalized seizures depending on the network structure. Counterintuitively, we found that decreasing connectivity between regions of the brain increased the frequency of seizure-like activity. Our findings may enlighten current controversies surrounding the concepts of focal and generalized epilepsy, and help to explain recent observations in genetic animal models and human epilepsies, where loss of white matter pathways was associated with the occurrence of seizures.

KEY WORDS: Primary generalized epilepsy, Secondary generalized epilepsy, Focal epilepsy, Network mechanisms, Computational model.

The International League Against Epilepsy (ILAE) Commission on Classification and Terminology has proposed a revised approach to classifying seizures and types of epilepsy (Berg et al., 2010). A fundamental conceptual shift is suggested, in which generalized and focal seizures are redefined as occurring in bilateral networks (generalized) and within networks either discretely localized or more widely distributed (focal). These proposals were designed to form a preliminary set of concepts toward a mechanism-based classification of the epilepsies, with brain networks and network structure providing a core foundation (Berg & Scheffer, 2011). This conceptual shift arises in the context of the widespread implementation of resting-state functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI), which have been used to study network structure and connectivity in the brain (Blumenfeld, 2005).

Studies of white matter connections in brain networks in epilepsy have typically revealed loss of white matter connectivity. For example, loss of white matter connectivity between hippocampus and connected limbic regions can be inferred from DTI studies of temporal lobe epilepsy (Focke et al., 2008); Chahboune et al. (2009) used DTI to demonstrate loss of transcallosal white matter tracts in both the Wistar albino Glaxo rats of Rijswijk (WAG/Rij) and genetic absence epilepsy rats of Strasbourg (GAERS) models of absence epilepsy. Similar findings have been observed in human studies, where, for example, (O'Muircheartaigh et al., 2010) observed reduction in the integrity of white matter tracts of the corpus callosum in patients with juvenile myoclonic epilepsy (JME).

Together these studies present the intriguing concept that abnormalities (typically involving loss of connectivity) within specific network structures of the brain are involved in the generation of seizures, rather than being a homogenous effect involving all regions simultaneously. The purpose of the present study is to describe the first steps toward a methodologic underpinning of the relationship between network structure and seizure type, directly inspired by the proposals of (Berg et al., 2010).

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To achieve this we use a computational model that describes phenomenologically the transitions from interictal to ictal dynamics based on the interplay between the dynamics of localized brain regions and the network structure between them. We use this model to explore the following questions: Can alterations in network structure support the electrophysiologic markers of focal and generalized seizures in the absence of a localized seizure onset zone? Does a localized seizure-onset zone with no alteration in network structure support the electrophysiologic markers of focal and generalized seizures? Can a loss of connectivity within a network of brain regions make seizures more likely?

Methods

The dynamics of networks of connected cortical regions was simulated using the phenomenologic model introduced and described in detail within (Benjamin et al., 2012). In the present manuscript, the model consists of a discrete set of four nodes with irregular directional connectivity, where each node was modeled using a mathematical equation that simultaneously permits both a ''normal'' resting state (interictal) and a high-amplitude oscillatory state (ictal), representing phenomenologically the most prominent EEG features of each state (Kalitzin et al., 2010). A model parameter controls the probability of transitions between these states for each individual node, with a very low probability of transition corresponding to a normal brain region and a high probability to a pathologic brain region (or ''seizure onset zone'').

Transitions between these two states are controlled by the interplay between intrinsic noise within each node and the synchronizing influences felt at each node as a consequence of its network connectivity. By ''synchronizing''—in this phenomenological context—we mean that a connection from region A to region B means that region A will influence region B toward the state occupied by region A. Within this framework we considered only the overall synchronizing effect of a connection between two regions and did not attempt to ascribe any relative contributions of underlying excitatory or inhibitory processes. These types of connections were partly inspired by the study of Warren et al. (2010), who studied synchronization in both the normal and focal epileptic brain, presenting evidence that the seizure-onset zone appeared disconnected from other nearby regions (calculated using mean-phase coherence). Simulations of the model were performed using a forward integration scheme (Euler-Maruyama) with a time step of 10^{-4}. Our analysis required approximately 10,000 simulations of up to 60-min (simulated) duration for each considered network; hence a high power supercomputer with 400 cores was used. Herein we limit our study to network structures that ensure there are no disconnected subnetworks. For a more comprehensive description of this computational model, we refer the reader to (Benjamin et al., 2012).

We used our computational model to explore mechanisms that underpin the electroencephalography (EEG) markers of primary generalized seizures, secondary generalized seizures, and focal seizures. By these we mean where the transition from interictal to ictal dynamics occurs either simultaneously across all regions in all events (primary generalized), predominantly in a single region but with some bursts involving all regions (secondary generalized), or almost always in a single region (focal).

Results

The starting point for each scenario was a four-region network, where the probability of interictal to ictal transition was very small (<<1 Sz/h). The parameters of each node were identical and the strength of each formed connection was the same. We found that either introducing a pathologic brain region (e.g., raising the probability of interictal to ictal transitions for an individual node) or altering network structure by removal of a connection between two regions could give rise to ''primary generalized'' seizures (Fig. 1). The subtlety of this effect is demonstrated in (Fig. 1C,D), where the occurrence of primary generalized seizures is crucially dependent on the choice of connection removed.

In Fig. 2 we consider the mechanisms of ''focal'' and ''secondary-generalized'' seizures. Again we started from a system of four normal brain regions, and studied the effects of introducing a pathological brain region and then removing first one and then two connections. Herein we observe dynamics consistent with either focal, secondary generalized, or primary generalized seizures, that are again dependent on the interplay between regional abnormality and network structures.

To address the relationship between loss of connectivity and the likelihood of seizures, we considered all 218 possible networks of four nodes that were distinct under permutations of nodes and edges. For each of these networks, we then calculated all unique networks that could be obtained upon removal of one connection. We then calculated the phenomenologic seizure frequency (the number of interictal to ictal transitions per unit of simulation time) and compared this for all combinations before and after removal of a connection. This resulted in 1,038 cases of which there were 659 where the rate increased following removal of a connection. On average the seizure frequency increased by 115% in these 659 cases. Of the 379 cases where the rate decreased, the average reduction in seizure frequency was only 13%. Together these results show that in general the likelihood of seizures substantially increased upon removing a connection, in keeping with experimental and clinical evidence that disconnected networks characterize epilepsies (Chahboune et al., 2009; Focke et al., 2008; O'Muircheartaigh et al., 2010).

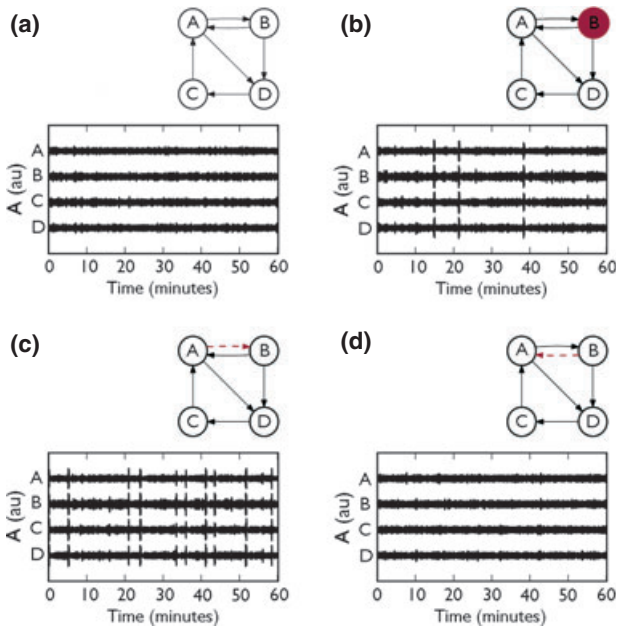

Figure 1.
Mechanisms of ''primary generalized'' seizure onset. Our starting point (panel **a**) was a system of four normal regions whose network structure did not support any transitions from interictal (noisy steady state) to ictal (large amplitude fluctuations) dynamics across the period of simulation. In panel (**b**) we introduced a pathologic brain region (mimicking a ''seizure onset zone'') by increasing the probability of interictal to ictal transitions in region (B). Despite no change in network structure, and an abnormality present in only one region, primary generalized events (where high amplitude deviations occur across all four regions) were generated. In panel (**c**) we investigated the effect of changes in network structure from the ''normal'' state, by first removing a unidirectional connection between region (A) and region (B) (the dashed line). This also resulted in primary generalized events. The subtlety of the effect of network disruption on seizure onset is illustrated in panel (**d**), where removal of the oppositely directed connection between (B) and (A) does not result in the occurrence of any events. The presented period of simulation is 1 h with the amplitude of the output plotted in arbitrary units.

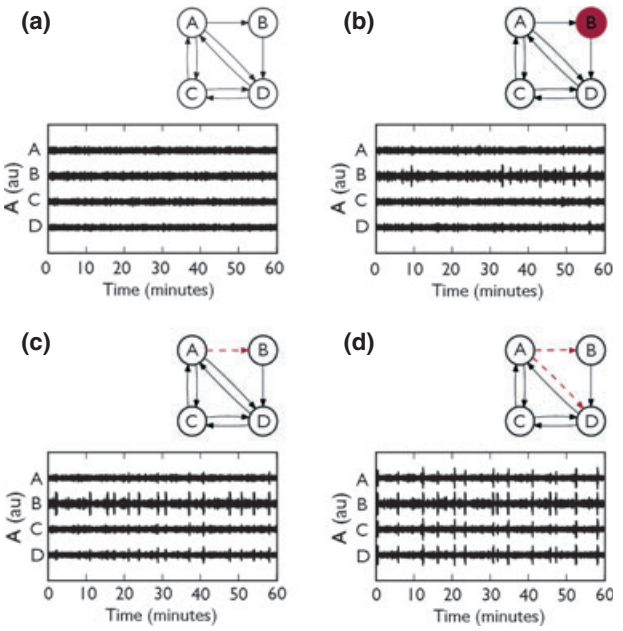

Figure 2.
Mechanisms of ''secondary generalized'' and ''focal'' seizure onset. Again our starting point (panel **a**) was a system of four normal regions whose network structure did not support transitions from interictal (noisy steady state) to ictal (large amplitude fluctuations) dynamics over the period of simulation. For this network, introducing a pathologic brain region with no alteration in network structure (panel **b**) resulted in focal seizure activity, where interictal to ictal transitions occurred within the pathologic region ((B)) only. In panel (**c**) we return to the case of four normal nodes but removed a specific unidirectional connection from (A) to (B), resulting in secondary generalized seizures (by which we mean there are frequent interictal to ictal transitions in region (B), which generalize to all other regions less frequently). Of note, this gives the appearance of pathologic activity arising in region (B), although in fact (B) has the same intrinsic properties as all other regions and is not a ''pathologic'' seizure-onset region. In panel (**d**) we remove a further unidirectional connection between (A) and (D) that results in frequent transitions across all regions (primary generalized). Were we to keep the pathologic region (B), then the interictal to ictal transitions in (**c**) and (**d**) occur more frequently, but do not change the seizure type. The presented period of simulation is 1 h with the amplitude of the output plotted in arbitrary units.

Discussion

We demonstrate that network structure can play a crucial role in determining whether seizure discharges, as characterized on a macroscale using EEG, can appear to be primary generalized, secondary generalized, or focal, and that this is independent of the existence of a single pathologic region (''seizure onset zone'') within the network. Of particular note is that either a subtle alteration in network or the introduction of a pathologic region in an otherwise normal network, can generate identical-appearing generalized activity (Fig. 1B,C). Furthermore, we observe that a change in network structure can give rise to a clearly focal onset in one brain region (Fig. 2C) when in fact the region is identical to all other regions within the brain.

We should emphasize that our model is phenomenologic; it includes no details of the physiology that underlies the functioning of the normal or diseased brain. Epileptogenesis has been explored previously in physiologic models with small-world networks (Netoff et al., 2004) as well as large-scale structural networks (Dyhrfjeld-Johnsen et al., 2007).

It would therefore be highly desirable to extend our findings to a more complex physiologic setting, for example, using a neural mass formulation (Deco et al., 2008) with a discretized network structure (Goodfellow et al., 2011) inferred from experimental or clinical recordings. This may enable a greater understanding of the underlying (patho)physiologic mechanisms of epilepsy seizure generation.

Finally, due to the phenomenologic nature of the model, we must be careful when addressing questions regarding driver/responder relationships. Our aim is primarily to illustrate how complex macroscale phenomena can arise, rather than an attempt to ascribe causality at this stage. All that said, our model makes a number of specific predictions that can be tested in both experimental (Chahboune et al., 2009) and human (O'Muircheartaigh et al., 2010; Focke et al., 2008) data. The model predicts that specific connectivity structures permit focal seizures to arise despite no seizure-onset zone (in the classically accepted context of a single abnormal brain region); and other connectivity structures permit primary generalized seizures to arise in the setting of a focal brain abnormality. The apparent paradox that loss of structural connections can give rise to seemingly generalized activity can be explained within our model by noting that networks with less connections are on average less stable, since the coupling between regions is synchronizing thus fewer connections make it more likely to exhibit transitions to ictal dynamics. We hope that these challenging ideas can be examined in the near future using the existing wealth of connectivity data from EEG, magnetoencephalography (MEG), fMRI, and DTI.

Disclosure

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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