Seizure 25 (2015) 160–166

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

How important is the seizure onset zone for seizure dynamics?

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ARTICLE INFO

Article history:
Received 31 July 2014
Received in revised form 9 October 2014
Accepted 21 October 2014

Keywords:
Epileptic networks
Seizure onset zone
Node importance
Graph analysis
Centrality

ABSTRACT

Purpose: Research into epileptic networks has recently allowed deeper insights into the epileptic process. Here we investigated the importance of individual network nodes for seizure dynamics.
Methods: We analysed intracranial electroencephalographic recordings of 86 focal seizures with different anatomical onset locations. With time-resolved correlation analyses, we derived a sequence of weighted epileptic networks spanning the pre-ictal, ictal, and post-ictal period, and each recording site represents a network node. We assessed node importance with commonly used centrality indices that take into account different network properties.
Results: A high variability of temporal evolution of node importance was observed, both intra- and interindividually. Nevertheless, nodes near and far off the seizure onset zone (SOZ) were rated as most important for seizure dynamics more often (65% of cases) than nodes from within the SOZ (35% of cases).
Conclusion: Our findings underline the high relevance of brain outside of the SOZ but within the large-scale epileptic network for seizure dynamics. Knowledge about these network constituents may elucidate targets for individualised therapeutic interventions that aim at preventing seizure generation and spread.

1. Introduction

Research over the last decade has provided strong evidence for the existence of epileptic (also referred to as epileptogenic) networks comprising cortical and subcortical areas in the genesis and expression of not only primary generalised but also focal onset seizures,[1–3] which has led to new concepts and terminology for classifying seizures and epilepsies.[4] A network (or graph) is usually considered as a set of nodes and a set of links, connecting the nodes. Functional (or interaction) brain networks can be derived from measurements of neural activity, and the connectedness between any pair of brain regions (nodes) can be assessed by evaluating interdependencies between their neural activities.

In addition to investigating structural alterations of epileptic brain networks, studies of functional alterations that make use of electroencephalographic recordings have identified network properties that provide new insights into global aspects of seizure dynamics [5–9] and the inter-ictal state.[10–13] In the majority of studies, methods from graph theory [14,15] had been employed which allow one to characterise global properties such as the clustering in an epileptic network, its efficiency to transport information, or the stability of the globally synchronised state.

There are by now only a few studies that investigated the relevance of local network properties for the dynamics of focal seizures.[5,16–18] The *importance* of nodes and links within the network is usually assessed with so-called centrality indices, and each of these indices characterises importance differently by taking into account the diverse roles nodes or links play in a network.[19–24] For patients with seizures arising from neocortex [16] or from focal cortical dysplasias,[17] most important network nodes have mainly been observed to coincide with the seizure onset zone (SOZ). These nodes have been interpreted as so-called network hubs that are assumed to play a leading role in the generation and propagation of ictal activity.[16,17] These findings, however, may be debated taking into account shortcomings of previous investigations (such as a limited number of seizures, a limited number of investigated brain regions, or usage of only one or a few centrality indices) as well as the many previous studies that reported on the high relevance of brain outside of the SOZ for seizure dynamics.[25,26,5,27–30]

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http://dx.doi.org/10.1016/j.seizure.2014.10.013
1059-1311/

Here, we investigated the importance of nodes in large-scale epileptic networks, derived from a large, heterogeneous set of focal seizures with different anatomical onset locations. By employing different but commonly used centrality indices,[31] we aimed at assessing a more comprehensive characterisation of importance of the SOZ, its neighbourhood, and of all other investigated brain regions during the pre-ictal, ictal, and post-ictal period. Our findings complement previous studies and extend the understanding on the role of different brain regions in the generation, propagation, and termination of seizures in large-scale epileptic networks.

2. Methods

2.1. Clinical data

The 52 patients (20 women, 32 men; mean age at the time of presurgical evaluation 36 ± 12 years, range 12–65; mean duration of epilepsy 24 ± 14 years, range 2–58) included in this retrospective study suffered from pharmacoresistant focal epilepsy with different anatomical onset locations that required invasive monitoring with intrahippocampal depth electrodes and subdural grid- and strip-electrodes (all manufactured by AD-TECH, WI, USA). Decisions regarding electrode placement were purely clinically driven and were made independently of this study. All patients signed informed consent that their clinical data might be used and published for research purposes. The study protocol had previously been approved by the ethics committee of the University of Bonn.

We analysed intracranial electroencephalographic (iEEG) recordings of 86 epileptic seizures, which were part of previous analyses.[6,32] They included 38 seizures with mesial-temporal, 22 with extra-mesial temporal, 19 with frontal, 5 with occipital and 2 with parietal lobe onset. There were 46 complex partial seizures without and 40 with secondary generalization as judged by studying seizure semiology on the accompanying video.

Using a Stellate Harmonie recording system (Stellate, Montreal, Canada; amplifiers constructed by Schwarzer GmbH, Munich, Germany) iEEG signals from, on average, 66 electrodes (range 26–124) were band-pass filtered between 0.1 and 70 Hz, sampled at 200 Hz using a 16 bit A/D converter, and referenced against the average of two electrode contacts outside the focal region. Reference contacts were chosen independently for each patient.

The peri-ictal recordings lasted, on average, 451 s (range 112–1702 s). The mean seizure duration amounted to 120.2 s (range 33.8–395.8 s), with seizure onsets and endings detected fully automatically using the method described by Schindler et al.[32] We assigned electrode contacts to three location categories, thereby making use of knowledge concerning location and extent of the SOZ, which is defined as the contacts where first ictal discharges were recorded.[33] Category *f* (*focal*) comprised all contacts located within the SOZ (on average 17.8% (2.6–52.4) of all contacts over all seizures and contacts) and category *n* (*nearby*) those contacts not more than two contacts distant to those from *f* (20.5% (1.0–96.0)). All remaining contacts were assigned to category *o* (*other*; 61.7% (0–93.0)).

2.2. Construction of functional networks

In order to construct functional networks from iEEG recordings, we associated each electrode contact with a network node and defined functional links between any pair of nodes *i* and *j*—regardless of their anatomical connectivity—using the cross-correlation function (see Appendix A) as a simple and most commonly used measure for interdependence between two signals.[6,34] iEEG data of each window were normalised to zero mean and unit variance. With a sliding-window approach (2.5 s window duration, 500 sampling points; no overlap) we calculated, for each seizure recording, a sequence of undirected, weighted functional networks spanning the pre-ictal, ictal, and post-ictal period.

2.3. Assessing node importance with centrality indices

Centrality indices (for details of calculation, see Appendix B) variously assess importance of individual nodes by considering e.g. a node's connectedness to other parts of the network or by its capability to influence other nodes through short paths. Degree centrality (or strength centrality ($\mathcal{C}^S$) in case of a weighted network) is defined as the number of links (or the sum of their weights) incident upon a node. A node with a high $\mathcal{C}^S$ is important since it interacts with many other nodes in the network. Eigenvector centrality ($\mathcal{C}^E$) recursively determines importance of a node not only on the basis of its links to other nodes, but also with respect to how those other nodes are linked (and so on). A node with high $\mathcal{C}^E$ is important since it has links to many other nodes that are themselves highly linked and central within the network. Closeness centrality ($\mathcal{C}^C$) expresses the average geodesic (i. e., shortest path) distance of a node to all other nodes. A node with high $\mathcal{C}^C$ is important since it can reach all other nodes in the network via short paths and may thus exert more direct influence over the nodes. Betweenness centrality ($\mathcal{C}^B$) is defined as the fraction of shortest paths between pairs of nodes that pass through a given node. A node with high $\mathcal{C}^B$ is important since it connects different regions of the network by acting as a bridge and thus can control the information flow in the network.

The complex spatial and temporal changes in frequency content are known to influence statistical properties of functional networks—such as clustering coefficient, average shortest path length and betweenness centrality—derived from seizure recordings.[8,16] In order to avoid spurious centrality estimates, that can trivially be related to spectral properties of the iEEG recording we applied a correction scheme (for details, see Appendix C), and in the following, we refer to these corrected centrality indices.

3. Results

With our analyses we observed a high variability of the various centrality indices for nodes in functional networks spanning the pre-ictal, ictal, and post-ictal period. In Fig. 1 we show, for each centrality index, temporal evolutions of the centrality values of a node from each of the three location categories for two focal seizures. From the nodes within each category, we show data from the one with highest average centrality over the course of the seizure. Interestingly, although the employed centrality indices rated importance of nodes differently, there was a rather close relationship between the temporal evolutions of $\mathcal{C}^S$, $\mathcal{C}^C$, and $\mathcal{C}^E$ (Pearson correlation coefficients ranged between 0.85 and 1.00) and these indices rated the same node from each location category as most important (highest respective centrality value). In contrast, $\mathcal{C}^B$ behaved differently and, with this centrality index, some prominent peaks could be observed for a node from the SOZ (category *f*) during both seizures.

During the course of the seizures, none of the sampled brain regions was rated as most and constantly important. We note that neither the described temporal evolutions of node centralities nor some prominent features could be regarded as exemplary for all investigated seizures. Nevertheless, the observed relationships between centrality indices were quite stable over all seizures (Pearson correlation coefficients (means and standard deviations); $(\mathcal{C}^S, \mathcal{C}^E) : 0.99 \pm 0.00$; $(\mathcal{C}^S, \mathcal{C}^C) : 0.89 \pm 0.18$; $(\mathcal{C}^S, \mathcal{C}^B) : 0.20 \pm 0.14$; $(\mathcal{C}^E, \mathcal{C}^C) : 0.87 \pm 0.18$; $(\mathcal{C}^E, \mathcal{C}^B) : 0.18 \pm 0.15$; $(\mathcal{C}^C, \mathcal{C}^B) : 0.21 \pm 0.15$).