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Evolving networks in the human epileptic brain

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HIGHLIGHTS

- We review analysis techniques for human epileptic brain networks.
- We summarize recent findings derived from studies investigating these networks.
- We point to possible pitfalls and open issues, and discuss future perspectives.

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ABSTRACT

Network theory provides novel concepts that promise an improved characterization of interacting dynamical systems. Within this framework, evolving networks can be considered as being composed of nodes, representing systems, and of time-varying edges, representing interactions between these systems. This approach is highly attractive to further our understanding of the physiological and pathophysiological dynamics in human brain networks. Indeed, there is growing evidence that the epileptic process can be regarded as a large-scale network phenomenon. We here review methodologies for inferring networks from empirical time series and for a characterization of these evolving networks. We summarize recent findings derived from studies that investigate human epileptic brain networks evolving on timescales ranging from few seconds to weeks. We point to possible pitfalls and open issues, and discuss future perspectives.

1. Introduction

Over the past decade, network theory has contributed significantly to improving our understanding of spatially extended, complex dynamical systems, with wide applications in diverse fields, ranging from physics to biology and medicine [1–15]. The human brain is an open, dissipative, and adaptive dynamical system, which can be regarded as a network of interacting subsystems. Due to its complex structure, its immense functionality, and – as in the case of brain pathologies – due to the coexistence of normal and abnormal functions and/or structures, the brain can be regarded as one of the most complex and fascinating systems in nature. The neocortex of human – a thin, extended, convoluted sheet of tissue with a surface area of approx. 2600 cm^2, and thickness 3–4 mm [16,17] – contains up to 10^{10} neurons, which are connected with each other and with cells in other parts of the brain by about 10^{12} synapses [18]. The length of all connections amounts to 10^7–10^9 m. The highly interconnected networks in the brain can generate a wide variety of synchronized activities, including those underlying epileptic seizures, which often appear as a transformation of otherwise normal brain rhythms.

With 50 million affected individuals worldwide [19,20], epilepsy represents one of the most common neurological disorders [21], second only to stroke. Epilepsy is defined as *a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition* [22]. For about 30% of epilepsy patients, seizures remain poorly controlled despite maximal medical management [23–26]. There is thus a strong need for new curative treatments [27,28].

An epileptic seizure is defined as *a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain* [22,29]. Epileptic seizures may be accompanied by an impairment or loss of consciousness, psychic, autonomic or sensory symptoms, or motor phenomena. Generalized-onset seizures are believed to instantaneously involve almost the entire brain [29], while focal-onset seizures appear to originate from a

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circumscribed region of the brain (*epileptic focus* [30,31]). These simplistic concepts of focal and generalized seizures, however, are being challenged by increasing evidence of seizure onset within a network of brain regions (*epileptic network*) [32–35]. This supports a new approach to classification of seizures and epilepsies [36].

The concept of an epileptic network comprises anatomically, and more importantly, functionally connected cortical and subcortical brain structures and regions. Since the timescale between onset and offset of a seizure is orders of magnitude smaller than that of any plausible change in the underlying structural components (such as neurons, axons or dendrites), seizures (and other related pathophysiological dynamics) may emerge from, may spread via, and may be terminated by network constituents that generate and sustain normal, physiological brain dynamics during the seizure-free interval.

Understanding the emergence of epilepsy and seizures from epileptic brain networks calls for approaches that take into account the interplay between the dynamic properties of nodes and the network structures connecting them. When investigating epileptic brain networks, nodes are usually assumed to represent distinct brain regions and edges represent interactions between them, and these nodes and edges constitute a *functional network.* Epileptic brain networks are *evolving functional networks* since their edges may change on various timescales, depending on physiological and pathophysiological conditions.

In this review, we summarize recent conceptual and methodological developments that aim at an improved inference and characterization of evolving epileptic brain networks. We highlight areas that are under active investigation and that promise to provide new insights into the complex spatial and temporal dynamics of these networks. We review frequently used approaches to infer functional networks from multichannel recordings of neural activities (Section 2) as well as network and node characteristics that are most commonly used for investigating epileptic brain networks (Section 3). In Section 4 we summarize findings obtained from studies that aim at characterizing evolving epileptic brain networks with respect to various physiological and pathophysiological conditions. Finally, in Section 5 we draw our conclusions and give an outlook.

2. Inferring functional brain networks

Functional brain networks are supposed to reflect the interaction dynamics between brain regions. Representing the complex system brain as a network, however, requires identification of nodes and edges. This is a challenging issue given the complex structural and functional organization of the brain – from the level of single neurons via microcolumns (containing some tens of neurons) and macrocolumns (consisting of some tens of microcolumns) to the level of brain regions, lobes, and functional brain systems – as well as methodological limitations in assessing this organization [37–45]. Brain regions (nodes) are usually associated with sensors that are placed to sufficiently capture the node dynamics. When characterizing edges, one is faced with the problem that the underlying equations of motion are not known and that interactions between brain regions cannot be measured directly. Thus, usually time series analysis techniques are employed to quantify linear or nonlinear interdependences between observables of brain regions.

2.1. Acquiring time series of neural activity

There are currently three recording techniques that are mainly used to obtain time series of neural activity, namely electroencephalography (EEG), magnetoencephalography (MEG), and functional magnetic resonance imaging (fMRI). Each of these techniques assesses different aspects of neuronal activity and has its own spatial and temporal resolution as well as its way of associating brain regions to network nodes.

With EEG [46] and MEG [47], electric and magnetic correlates of neural activities outside the head are measured with sensors that are placed according to standard schemes. In some epilepsy patients undergoing presurgical evaluation [30], sensors are placed intracranially, which allows for directly recording neural activities from within deeper brain structures and from the surface of the brain (iEEG) [48]. In the following we use EEG for both, surface and intracranial EEG. For all recording techniques, volume conduction and dense spatial sampling can give rise to mostly unavoidable influences like transitivity and common sources (see Section 2.2), which need to be addressed in subsequent analysis steps. For EEG the recording montage together with the choice of a reference electrode is a notoriously ill-defined problem [49–51]. An important advantage of EEG is the ability to perform recordings over extended periods of time (days to weeks), such that a wide spectrum of physiological and pathophysiological activities can be captured. EEG and MEG sample brain activities with a time resolution of a few milliseconds, and sensor placement limits spatial resolution besides the mentioned influences.

With fMRI [52] neural activity is assessed indirectly via associated changes in blood oxygenation. While this can be captured with very high spatial resolution, the temporal resolution is orders of magnitude lower than with EEG or MEG.

2.2. Estimating interactions from time series

A plethora of analysis techniques is available to estimate strength and direction of interactions from time series. These estimators originate from synchronization theory, nonlinear dynamics, information theory, statistical physics, and from the theory of stochastic processes (for an overview, see Refs. [53–60]). Here we highlight some of the more recent developments and improvements.

When analyzing interactions between several systems, one may be faced with the problem of *transitivity:* many estimators do not allow for distinguishing between direct and indirect interactions [39,61] and therefore spurious edges between network nodes may be inferred. This issue has been addressed through the use of partialization techniques [62–68] but their suitability for analyses of empirical data remains to be shown. Another frequently arising difficulty is due to the problem of *common sources* [39,43]: sensors which are spatially close are likely to pick up very similar activities. This can lead to spuriously high estimates of strengths of interactions but can probably be avoided using more advanced estimators for phase synchronization [69,70]. Other developments that promise to further advance characterization of interactions include an optimized mixed state-space embedding [71], improved phase determination [72–76], bivariate surrogates [77–80], usage of ranks for nonlinear interdependences [81], cross-frequency decomposition [82], improved recurrence estimators [83], multivariate and delayed information transfer [84–88], and approaches that characterize interactions even for transient dynamics [89–91]. We note that up to now there are no commonly accepted approaches to estimate interactions and their properties from time series.

The human brain is certainly a non-stationary system, but for most estimators at least approximate stationarity is required. Therefore it is advisable to perform a time-resolved analysis, which is carried out via a sliding-window approach. A trade-off has to be made between approximate stationarity and the required statistical accuracy for the calculation of the estimator. Typically, windows spanning several tens of seconds of brain activity are assumed to be acceptable [92–94]. For each of these windows, an