Capturing time-varying brain dynamics

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Abstract. The human brain is a complex network of interacting nonstationary subsystems, whose complicated spatial-temporal dynamics is still poorly understood. Deeper insights can be gained from recent improvements of time-series-analysis techniques to assess strength and direction of interactions together with methodologies for deriving and characterizing evolving networks from empirical time series. We here review these developments, and by taking the example of evolving epileptic brain networks, we discuss the progress that has been made in capturing and understanding brain dynamics that varies on time scales ranging from seconds to years.

Keywords: brain dynamics / evolving networks / synchronization / nonstationarity / direct/indirect interactions / network characteristics / time-series analysis / EEG / epilepsy

1 Introduction

Due to its complex structure and its immense functionality, the human brain is one of the most complex and fascinating systems in nature. The neocortex of human is a thin, extended, convoluted sheet of tissue with a surface area of approx. 2600 cm² and thickness 3–4 mm [1,2]. It contains up to 10¹⁰ neurons (and about three times more glia cells [3]), which are connected with each other and with cells in other parts of the brain by about 10¹² synapses [4]. The length of all connections amounts to 10⁷–10⁹ m. The highly interconnected networks in the brain, which are neither random nor entirely regular, span multiple spatial scales, from individual cells and synapses via cortical columns to (sub)cortical areas. These networks support a rich repertoire of behavioral and cognitive functions [5–17] that are – for the most part – shared among all individuals, despite enormous differences in morphology and connection structure. Moreover, in the case of brain pathologies, normal and abnormal functions and/or structures can coexist [18–20].

In humans, macroscopic brain dynamics can be assessed non-invasively with three major recording techniques, namely electroencephalography (EEG) [21], magnetoencephalography (MEG) [22], and functional magnetic resonance imaging (fMRI) [23]. While EEG and MEG capture electric and magnetic correlates of gross neural activities outside the head, fMRI assesses these activities indirectly via associated changes in blood oxygenation. In

some epilepsy patients that undergo presurgical evaluation [24], invasive intracranial EEG (iEEG) provides access to the meso- ($\approx 10^5$ neurons) and the micro-scale (single neurons) [25–28] via electrodes implanted chronically on the surface of the brain and/or within deep brain structures (e.g., the hippocampus). Each of these techniques has its own temporal and spatial resolution. EEG/iEEG and MEG sample brain dynamics with a high time resolution (typically a few milliseconds), and spatial resolution is limited by sensor placement. fMRI allows for a higher spatial resolution but the temporal resolution is orders of magnitude lower than with EEG or MEG. At present, EEG/iEEG is the only technique that allows for the continuous multichannel recording of time series of brain dynamics over extended periods of time (days to weeks), such that a wide spectrum of physiological and pathological physiological activities can be captured.

Despite access to the various spatial scales, both the respective dynamics and particularly the mapping between them are not fully understood. EEG/iEEG time series exhibit oscillations at a variety of frequencies and these oscillations are thought to represent synchronized activity over a network of neurons [21]. Several of these oscillations have characteristic frequency ranges and spatial distributions and can be associated with different states of brain (dys)functioning (e.g., waking, various sleep stages, focal epileptic seizures). Recent investigations that simultaneously assess dynamics from the macro- (gross neural activities) and the micro-scale (single/multi-neuron activities) point to complex relationships between these scales, and combining insights from both these dynamics is a key challenge for the future [29].

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Another characteristic of brain dynamics, which contrasts the aforementioned *oscillation-based* view to brain (dys)functioning, is that it appears to not contain a predominant temporal scale [30]; rather time series exhibit a $1/f^\alpha$ -like power spectrum (with $\alpha \in [1, 3]$) at many spatial-temporal scales [12,31–34]. Such a *scale-free* dynamics, coexisting with an oscillatory one, has long been considered as brain noise, but there is now increasing evidence that parameters of this dynamics are closely related to brain (dys)functioning [35,34].

These various, apparently irregular dynamics might point to nonlinear generating mechanisms. Indeed, in the brain, nonlinearity is already introduced on the cellular level – given that the dynamical behavior of individual neurons is governed by integration, threshold, and saturation phenomena [36]. It might, however, not be valid to expect that a huge network of such nonlinear elements also behaves in a nonlinear way [37,38]. Despite a number of approaches to test for nonlinearity [39,40], compelling support for nonlinearity in brain dynamics on the meso- and macro-scale as well as for any brain (dys)functioning has as yet not been provided. A prominent counterexample is epilepsy, for which abundant evidence for nonlinear brain dynamics not only during seizures but also during the seizure-free interval has been produced (see, e.g., [41–55]).

Since the brain is a complex network of interacting nonstationary subsystems, its spatial-temporal dynamics is also influenced by properties of such interactions. Indeed, interactions mediated by synchronization phenomena on various scales were shown to correlate with perceptual binding, and specific synchronization patterns appear to be directly related to behavior and cognition [8,11]. Conversely, abnormal patterns of synchronization seem to be a key pathophysiological mechanism underlying various neurological and psychiatric disorders, such as epilepsy, schizophrenia, dementia, and Parkinson’s disease [18–20]. It is, however, not yet clear which of the many forms of synchronization known from physics (for an overview, see, e.g., [56–59]) best characterizes brain (dys)functioning.

A large number of time-series-analysis techniques – which are based on different mathematical and physical concepts – is available (see, e.g., [56,60–76]), and these techniques are highly suitable to further improve the characterization of brain dynamics. Depending on whether the employed technique is used to characterize the dynamics sampled at a single recording site or relations between dynamics sampled simultaneously at two or more sites, it is referred to as a univariate, bivariate, or multivariate time-series-analysis technique, respectively. Such techniques provide various indices that allow characterization of different properties of some dynamics and of properties of interactions between two or more systems. Univariate time-series-analysis techniques that assess nonlinear properties of brain dynamics such as complexity or fractality were evaluated in a number of reviews (see, e.g., [77–82]). Here, we discuss recent developments of (mostly bivariate and multivariate) time-series-analysis techniques that allow construction and characterization of weighted and directed, evolving

large-scale functional brain networks, which can contribute to gain deeper insights into cooperative phenomena that are supposed to underly brain (dys)functioning.

We begin with a brief overview of commonly used approaches to tackle the problems one is confronted with when investigating inherently nonstationary brain dynamics on various spatial and temporal scales. We then discuss time-series-analysis techniques that allow a data-driven characterization of interactions between two or more simultaneously sampled brain regions and that form the basis for constructing evolving functional brain networks from multichannel recordings of brain dynamics. We proceed with concepts and indices from network/graph theory that are frequently used to characterize statistical and spectral properties of these networks. Given that the significance of indices for interaction and network properties can be affected by influencing factors from various sources, we then discuss approaches for surrogate testing that can help eliminating or at least minimizing those influences. Before we draw our conclusions, we illustrate recent efforts on characterizing aspects of human epileptic brain dynamics varying on time scales spanning up to seven orders of magnitude.

2 Tackling nonstationarity

The human brain is an open, dissipative, and adaptive dynamical system and thus inherently nonstationary. This property is usually regarded as an obstacle, although nonstationarity might actually represent an interesting aspect of the dynamics [83–85], and the vast majority of time-series-analysis techniques require the system to be (at least approximately) stationary in order to allow for a robust and reliable characterization.

For long-lasting recordings of ongoing brain dynamics, the most common way of dealing with nonstationarity is to apply a sliding-window analysis (see Fig. 1A), thereby cutting the time series of an appropriate observable into successive (non)overlapping segments (or windows) during which dynamics of the system can be regarded as approximately stationary. A characterizing index is then calculated for each data window. Various methods have been proposed to assess the length of a window (see, e.g., [49,83,84,86–93]) and findings range between a few hundreds of milliseconds to some tens of seconds. When using shorter windows, one needs to take into account that the decreased number of data points entering some algorithm may increase the uncertainty of a characterizing index. Thus, the choice of a window length is often a compromise between the required statistical accuracy for the estimation of indices and approximate stationarity within a window length.

Other techniques make use of multiple realizations of the corresponding short-lasting (typically a few 100 ms) transient dynamics (e.g., recordings of evoked or event-related potentials/fields [94]). By replacing the temporal average with an ensemble average, these techniques allow for a time-resolved analysis of the transient dynamics [95–98].

Fig. 1. Schematic of interaction-analysis-based approaches to characterize time-varying brain dynamics. (A) Sliding-window analysis: long-lasting multichannel recordings of brain dynamics (here: intracranial EEG) are segmented into successive (non) overlapping windows; T_n denotes the time point associated with the left boundary of the n th window (marked in gray). (B) Time-dependent sequence of interaction matrices: each matrix contains estimates of an interaction property (strength or direction) calculated from the brain dynamics within a given window for all pairs of N sampled brain regions. (C) A bivariate analysis approach renders a time-dependent sequence of an interaction property (here: strength of interaction) for each pair of sampled brain regions (upper three sequences are shifted upwards to enhance readability). (D) A network analysis approach renders a time-dependent sequence of a local or global network characteristic. Time-dependent sequences depicted in (C) and (D) are then subject to further analyses.

3 Characterizing interactions

As already mentioned above, a large repertoire of analysis techniques – derived, e.g., from statistics, nonlinear dynamics, synchronization theory, and statistical physics – is available that allow one to characterize interactions between two or more systems (here: brain regions). Here we consider some of the general aspects and recent developments for inferring interactions from multichannel time-series data.

An interaction between two observed, possibly nonlinear dynamical systems is usually characterized by its strength and its direction, and these properties can be assessed with analysis techniques based on different concepts, such as (statistical) correlation [99], predictability [100,101], information flow [102,103], phase synchronization [104,105], or generalized synchronization [51,106–108], to name just a few. Since each concept relies on certain characteristic features of the dynamical systems under investigation and thus captures different aspects of an interaction, the use of the respective analysis techniques for

an investigation of interaction properties depends on the specific problem. In the neurosciences, and particularly in context of functional neuroimaging, the characterization of interactions is often based on the so-called brain connectivity approach that relates structure to function (and vice versa) [109]. *Structural connectivity* describes physical (and chemical) connections between neuronal populations or individual neurons. *Functional connectivity* describes the (statistical) dependence (or similarity) between signals recorded from some neuronal units regardless of whether these units are connected by direct structural edges. *Effective connectivity* requires formulation of a mechanistic model of the causal effects upon which the data to be observed are based, and may be viewed as a union of the aforementioned concepts. Inferring causality – particularly from short and noisy signals – is notoriously problematic.

We note that many indices, particularly those that characterize the strength of an interaction, were shown to be somewhat correlated with each other in comparative studies using both model dynamical systems [110,111] and EEG/iEEG recordings [112–114]. Nevertheless, since interaction properties may vary considerably over time [114,115] (see Fig. 2), it is advisable to employ analysis techniques from various concepts to allow for a comprehensive characterization.

Despite being based on a common concept, most techniques assess either exclusively the strength or the direction of an interaction, and in many cases estimators may depend differently on type and strength of coupling [115–119]. As an example (see Fig. 3), in some driver–responder system, estimates for the strength of an interaction increase monotonically with an increasing coupling strength until they saturate in the limit of strong couplings. Estimates for the direction of an interaction also increase, but only up to some maximum at intermediate coupling strengths and eventually vanish in the limit of strong couplings. This reflects the fact that the dynamics of coupled systems become almost indistinguishable in the limit of strong couplings, but estimators for the direction of an interaction require some form of distinguishability. It has been suggested that further insights into how estimators depend on type and strength of coupling may be gained with data-driven methods that aim at extracting and reconstructing the coupling functions between interacting systems [120–124].

If interactions are to be characterized between more than two systems (i.e., a network composed of multiple coupled systems), the aforementioned concepts and their analysis techniques can – in general – be applied to all pairs of systems, which leads to an interaction matrix $\mathbf{I}$ that represents a network (see Fig. 1B and next section). Despite being widely used in various scientific disciplines, with this approach one might be faced with the demanding problem to distinguish between direct and indirect interactions (mediated by another – even unobserved – system), which can lead to severe misinterpretations of possible causal relationships. In order to overcome this problem of transitivity, various analysis techniques based on partialization analysis have been proposed (see, e.g., [125–144]). All these techniques involve calculating properties of an interaction between two systems, holding constant the external influences of a third. Nevertheless, one needs to take into consideration that

volume conduction and asymmetric signal-to-noise ratios [145,146] as well as the number of interacting systems and connection density [147–149] appear to severely limit the efficiency of many techniques. More recent approaches to distinguish between direct and indirect interactions include concepts from network theory as well as assumptions regarding the network topology and causality [150–156], but their suitability for the analysis of brain dynamics remains to be shown.

Another and closely related issue are spurious indications of strength and direction of interactions, which can be caused by sampling the same subsystem, i.e., a common source, and that can also lead to severe misinterpretations. Such an instantaneous mixture of activities from multiple sources may be caused by, e.g., a too close spatial sampling of some brain region or – as in case of EEG recordings – due to the unavoidable referential recording. Extensions to and modifications of particularly phase-based approaches [157–160] have been proposed that appear to be much less affected by the influence of common sources, their suitability for analyses of brain dynamics, however, continues to be matter of debate [161–165].

Before closing this section, we mention other developments that are of importance to further improve characterization of interacting brain systems. Given that axonal delays between brain areas can amount to several tens of milliseconds, recently proposed analysis techniques to detect and to characterize time-delayed directional interactions [166–170] can help to better interpret the direction of interactions between brain regions. Last but not least, scale-bridging analysis techniques for characterizing couplings between point processes and flows [171] can help to better understand interactions between the single-neuron level and the neuron-network level.

4 From pairwise interactions to functional brain networks

As already mentioned in the previous section, the aforementioned concepts and their analysis techniques can be applied to characterize interactions between multiple coupled systems, from which an interaction matrix $\mathbf{I}$ – that represents a network – can be derived (see Fig. 1B). Indeed, research over the last decade indicates that with this ansatz so called functional brain networks can be derived from multichannel recordings of neuronal activities (see, e.g., [172–174] for an overview). Brain regions (nodes) are usually associated with sensors that are placed to sufficiently capture the node dynamics, and edges represent interactions between pairs of nodes. These nodes and edges constitute a functional brain network. This initial definition of network constituents, however, can have profound consequences for how functional brain networks are configured and interpreted [175–182]. Moreover, it remains unclear which analysis techniques best represents the underlying neurobiological reality.

The interaction matrix $\mathbf{I} \in \mathbb{R}^{N \times N}$, where N denotes the number of nodes, usually serves as starting point for the construction of binary or weighted and undirected or directed networks. An undirected binary network characterizes interacting brain regions in terms of *connected* or

Fig. 2. Exemplary time-dependent sequences of mean interaction strength and various network characteristics. Sequences derived from multichannel ($N=90$), long-term (14.7 days) iEEG recordings from a patient with a focal epilepsy undergoing presurgical evaluation (the patient signed informed consent that the clinical data might be used and published for research purposes, and the study protocol had previously been approved by the ethics committee of the University of Bonn). From top to bottom: mean interaction strength $\bar{R}$ (average over all estimated strength values – calculated using the mean phase coherence R [105] – from all pairs of sampled brain regions), assortativity a , clustering coefficient c , synchronizability s , betweenness centrality C^B of an exemplary brain region near the seizure-generating area, and betweenness centrality C^B of a homologous region in the opposite brain hemisphere. Left column shows full sequences (smoothed with a moving average over 40 windows (13.65 min) to improve legibility, and ticks on x -axis denote midnight); right column shows zooms in (1 h segment from day 1) of the unsmoothed sequences. Grey bars mark discontinuities in the sequences due to recording gaps.

disconnected and can be described by a symmetric adjacency matrix $\mathbf{A} \in \{0, 1\}^{N \times N}$. An entry A_{kl} in this matrix is 1 if there is an edge between nodes k and l , and 0 otherwise. Typically, two nodes are assumed to be connected by an edge, if an estimator for the strength of interaction exceeds some threshold Θ . As of now, there are no commonly accepted criteria for the choice of Θ [176,183–187]. Alternatively, one can derive a minimum spanning tree from the interaction matrix and use it as adjacency matrix [188–191].

It is often of interest how strongly nodes interact with each other. This can be characterized by an undirected weighted network, which can be described by a symmetric weight matrix $\mathbf{W} \in \mathbb{R}_+^{N \times N}$. While it is possible to again define some threshold to exclude edges with non-significant interaction strengths, in most cases all edges are considered to exist in such a complete network. The most direct way to determine the weight matrix $\mathbf{W}$ is to assume identity between a weight and the estimated strength of an

Fig. 3. Schematic dependence of strength and direction of an interaction on coupling strength. Estimates for the strength (red, solid line) and direction of an interaction (blue, dashed line) for some driver-responder system evaluated for increasing coupling strengths.

interaction, i.e., $W_{kl} = I_{kl}$. Albeit most estimators for the strength of an interaction are normalized, in general, the weight matrix is not; a suitable normalization of this matrix is thus advisable. Eventually, dominant influences of the distribution of estimated strengths of interaction on network properties of interest [192] can be minimized by assigning weights to the edges using ranks of the entries of $\mathbf{W}$ [193].

Directed functional brain networks have been investigated only rarely (see, e.g., [194–196]). Expanding a binary network to a directed binary network appears intuitive. Borrowing from the construction of the undirected case, an estimator for the direction of interaction can be thresholded to exclude non-significant directionality indications and to derive a directed adjacency matrix $\mathbf{D} \in \{0, 1\}^{N \times N}$. In this asymmetric matrix an entry D_{kl} is 1, if there is a directed edge from node k to l , and 0 otherwise. If the entry of the inverse direction D_{lk} is also 1 ($D_{kl} = D_{lk} = 1$), the edge is called bidirectional. One should keep in mind though, that there are no commonly accepted criteria for the choice of the threshold. Assuming identity between a directed edge and the estimated direction of an interaction, $D_{kl} = I_{kl}$ is problematic given the lack of physical interpretability of an estimator's modulus; in many cases only the sign indicates the direction.

Merging both interaction properties – strength and direction – into a weighted and directed network is more complex and, as yet, not solved in a conclusive manner. For such a network, it is necessary to remember that strength and direction are different but not unrelated properties of interactions [115]. Quite often has the modulus of an estimator for the direction of an interaction been interpreted as the strength of an interaction, which might not generally be valid and particularly for uncoupled and strongly coupled systems can lead to severe misinterpretations [115, 116, 118]. It is therefore advisable to estimate both interaction properties separately but using methods that are based on the same concept (e.g., synchronization theory or information theory), as it is unclear how different concepts translate to each other. Moreover, it is necessary to define how the weights should be allocated to forward and backward direction of the edges, as strength of interaction is invariant under exchange of nodes, while direction of interaction is not.

With a chosen network construction approach and using a sliding-window analysis, a sequence of functional brain networks – a so called evolving brain network with fixed nodes and time-varying edges – is usually derived, whose further characterization is discussed in the next section.

5 Characterizing evolving brain networks

Characteristics of networks are assessed with approaches from graph theory (see [58, 173, 197–200] for an overview). In the following, we concentrate on those characteristics that are frequently determined when investigating an undirected binary or weighted evolving brain network (extensions to directed networks are subject of current research). Characteristics can be divided into *local* ones, which describe properties of parts of the network, e.g., individual nodes or edges and into *global* ones, which assess properties of a network as a whole. Having determined the temporal sequence of some network characteristic (see Fig. 1D), this sequence is then subject to further analyses (e.g., using linear or nonlinear time-series-analysis techniques).

In a binary network, the *degree* of a node is the number of edges incident to it, while in a weighted network the *strength* – the sum over the weights of all edges incident to that node – is used instead. Degree and strength are often used as indicators for the connectedness of nodes or to assess the importance of a node (see below).

In a binary network, the *shortest path* between two nodes l and k is the smallest number of edges one has to traverse to reach node l from node k . The *diameter* of a network is the longest of all shortest paths. In a weighted network, defining the length of a single path between two nodes is not straightforward, but quite often is the inverse of the edge weight used as length since the ratio between the weights of two edges is the same as the ratio between their lengths. The *mean shortest path* is the mean over all shortest paths in a given network. For an unconnected network (no path exists between some nodes k and l) the mean shortest path will diverge. The easiest and most often applied ansatz to circumvent this problem is to ensure that the network is always connected (e.g., by choosing an appropriate threshold for network construction). Recent studies indicate that the shortest path is also affected by other influencing factors such as common sources and indirect interactions [184, 201]. The mean shortest path is often used to assess the efficiency of information or mass transport on a network.

In a binary network, the (*local*) *clustering coefficient* of a node is the ratio of that node's neighbors that are connected to each other. Taking the mean over all nodes gives an estimate for the (*global*) *clustering coefficient* of that network. The sometimes employed concept of *transitivity*, defined as the rate at which nodes with a common neighbor are connected, is not the same as the clustering coefficient, though similar. Several suggestions have been made to extend the concept of a clustering coefficient to weighted networks [202], but their suitability for the analysis of evolving brain networks remains to be shown. Similar to the mean shortest path, the clustering

coefficient is prone to influences resulting from over-sampling and common sources [184,201]. The clustering coefficient is often used to assess the robustness of a network to deletion of individual nodes.

Clustering coefficient and mean shortest path are often employed to determine whether a network is a small-world network or not [203]. This property has repeatedly been reported for both structural and functional, physiological and pathophysiological brain networks [172,204,205]. With the identification of factors that influence clustering coefficient and mean shortest path, however, these findings continue to be matter of considerable debate [175,177,182,206].

The tendency of nodes to connect to other nodes with similar properties is called *assortativity*. In the context of functional brain networks, most often the preference to connect to nodes with similar degrees is investigated. Such degree-degree correlations have far-reaching consequences for network resilience (assortative networks are less vulnerable to attacks [207]), for the ability of a network to globally synchronize (assortative networks are harder to synchronize), and the tendency of a network to separate into distinct groups (assortative networks have a stronger tendency to do so) [208].

Synchronizability describes the stability of the global synchronization state, i.e., the propensity of a network of coupled dynamical systems for synchronization. This property can be derived from the eigenvalue spectrum of the graph Laplacian via the ratio of the largest and the second smallest eigenvalue (for an overview, see, e.g., [209,210]).

The concept of *centrality* assigns an influence or importance to some node. Various centrality indices had been proposed and each of these indices capture different aspects of importance within a network [211,212]. Nodes with high degree (or strength) centrality (see above) are often called *hubs*. *Closeness centrality* is the average of the distances (i.e., shortest paths) of a node to all other nodes. Degree and closeness centrality thus consider nodes which are better connected to the rest of the network. In contrast, *betweenness centrality* is defined as the ratio of all shortest paths (between all nodes) passing through a given node. A node with a high betweenness centrality is important for connecting different regions of the network by acting as a bridge. *Eigenvector centrality* for node i is defined as the i th element of the eigenvector to the largest eigenvalue of the adjacency matrix $\mathbf{A}$. Through this recursive definition, it has high values for nodes that are connected to other nodes with a high eigenvector centrality.

We note that the aforementioned centrality indices can be defined analogously for edges. Moreover, the characterization of networks based on minimum spanning trees may require additional indices.

6 Surrogates, null models, and network comparison

Characteristics of time series and evolving networks can be affected by a number of influencing factors, which can lead to severe misinterpretations. Such factors may arise from specifics of the applied recording technique, from specifics

and uncertainties of the various analysis methods, from the way networks are derived from multichannel time-series data, or may be due to unavoidable noise contaminations. An elimination or at least a minimization of those influences can be achieved through surrogate testing. This statistical approach requires the formulation of a null hypothesis [213], which specifies properties of influencing factors that might lead to the results of an analysis. An ensemble of surrogate data – Monte Carlo-simulated [214] instances of an appropriate null model – is then generated, which preserves all important statistical properties of the original data but not the property which is tested for. The null hypothesis will be accepted if some discriminating statistics for the original data falls within the expectation range for the surrogate ensemble.

Surrogate-generating concepts and algorithms are available that can be applied on the level of time series or on the network level. These are briefly described in the following.

A large number of techniques is available to generate surrogates for multichannel time-series data (see, e.g., [39,40,215] for an overview). When investigating oscillatory brain dynamics, particularly Fourier-based surrogate techniques are prone to false rejections of the null hypothesis due to quasi-periodicities or coherency, and various extensions have been proposed that aim at minimizing the risk for false rejections [216–218]. Alternatives to such surrogate techniques are based on the wavelet transform [219–221] or on recurrence plots [222]. Techniques that take into account long-term fluctuations [223,224] or other forms of nonstationarities [225,226] may prove helpful when analyzing interactions in multichannel recordings that extend over longer time periods (hours to days to weeks).

On the network level, one may want to test first how the way functional networks are derived from time-series data affect findings. To this end, the results of the whole analysis procedure can be compared to those for surrogate time series [177,201]. Characteristics of the derived networks can then be compared to those that can be expected for null model or surrogate networks that constrain specific properties [173]. Eventually, an appropriate surrogate normalization of the specific network characteristics can aid with their interpretation, and thus can prevent deriving inappropriate conclusions (see, e.g., [192] and references therein).

When investigating time-dependent networks, it is often of interest, how networks change from time step to time step, which requires some form of comparative analysis between networks [176]. Such an analysis, however, is highly nontrivial, given that topological properties of a given network are necessarily dependent on the number of edges and the number of nodes, each of which may change over time, rendering an unbiased comparison between networks difficult. An improved testing for differences between time-evolving networks may be achieved with distance metrics [227–230] or with other recently proposed methods for generating surrogates for time-evolving networks [231–233].

7 Capturing time-varying dynamics in the human epileptic brain

Electroencephalographic recordings (either non-invasive or invasive) from epilepsy patients are particularly suitable for an investigation of time-varying brain dynamics on various spatial and temporal scales. During clinical monitoring for epilepsy surgery such recordings are usually performed over extended periods of time (days to weeks), with high spatial and temporal resolution. Moreover, the recent development of an ambulatory seizure advisory system [234] allowed to record invasively electrical activity of the brains from epilepsy patients for a period of several years. Long-term recordings capture a wide spectrum of physiological and pathophysiological activities as well as interactions between these activities. In the following, we briefly illustrate some recent findings that have been achieved by analyzing such recordings.

A large number of studies investigating long-term recordings from epilepsy patients is concerned with the question whether information predictive of an impending seizure can be extracted from ongoing EEG/iEEG signals using univariate, bivariate, or multivariate analysis techniques (see, e.g., [235–238] for an overview). Findings achieved so far indicate that, at least in some patients, pre-seizure states can indeed be identified with various techniques well ahead of seizure occurrence. Pre-seizure changes in the time-dependent sequence of some characteristics, however, may also be identifiable – but through less pronounced changes – during the seizure-free interval. It thus remains unclear whether identification performance suffices for clinical applications of prediction-based seizure-prevention techniques [239]. Given the heterogeneity of seizures and epilepsies, successful state identification probably requires a combination of various univariate and bivariate, both linear and nonlinear, analysis techniques. In a recent seizure-forecasting contest [240], a large number of spectral EEG properties together with various machine-learning algorithms were reported to perform better than some random predictor on a large iEEG database from canines and humans with epilepsy. Although such a contest allows to directly test and compare various seizure-forecasting strategies, the multiple testing [241] of a plethora of algorithms requires a reasonable control of the type-I error. In addition, findings unfortunately add little – if at all – to our understanding of possible neurophysiological mechanisms associated with pre-seizure changes.

Other studies aim at pinpointing factors that might influence the identification of pre-seizure states, such as seizure occurrences, changes in antiepileptic medication, the circadian rhythm, to name just a few. Inter-seizure intervals of more than 10 000 seizures (derived from long-term (up to 2 yrs) ambulatory intracranial EEG recordings) were reported [242] to follow a power-law distribution [243] with an exponent indicative of long-range memory in human seizure frequency. This observation was also supported by estimated Hurst exponents H in the range $0.5 < H < 1$, and the observed memory spanned time scales from 30 min to 40 d. This finding is in stark contrast to the notion that timing and occurrence of seizures can best be described by a Poisson process [244,245].

Changes in cortical excitability are believed to play a role in normal conditions during the sleep-wake cycle, while pathological changes are closely related to initiation and spread of seizure activity. Cortical excitability – characterized from the ongoing EEG/iEEG with bivariate indices for synchronization – was reported [246] to correlate well with the load of antiepileptic drugs (used to control the degree of cortical excitability) and to exhibit a characteristic modulation over 24 h, progressively increasing during wakefulness and rebalanced during sleep. Together with an earlier report on a brain-region-dependent impact of the circadian rhythm [247], these findings indicate that EEG-based indices for synchronization can probably be regarded as a reliable characteristic for excitability.

There is increasing evidence for epilepsy to be a network disease (see, e.g., [72,173,248,249] for an overview), with relevant interactions extending well beyond the seizure-generating brain structure (epileptic focus or epileptogenic zone). With this concept, seizures (even focal ones) and other related pathophysiological dynamics are regarded as emerging from, spreading via, and being terminated by network constituents that generate and sustain normal, physiological brain dynamics during the seizure-free interval. Deeper insights into epileptic networks and their dynamics can be achieved by investigating – at various scales – characteristics of functional brain networks derived from epilepsy patients. A number of studies of functional brain networks during seizures reported various local and global network characteristics to provide important clues about seizure dynamics, how they spread and terminate (see, e.g., [208,250–260]). These findings – exhibiting a high similarity of topological evolution across different types of epilepsies, seizures, medication, age, gender, and other clinical features – are of high relevance for further improving existing seizure-prevention techniques or for developing new ones, based, e.g., on behaviorally induced modifications of epileptic networks [238,261,262]. As regards the seizure-free interval, most studies investigated functional brain networks that were derived from selected EEG/iEEG epochs that ranged from some seconds to a few minutes only (see [263] for an overview), and only rarely [256,264–267] had the evolution of an epileptic network been monitored over longer periods (days to weeks; for an example, see Fig. 2). These studies reported on characteristic modulations of local and global network characteristics over 24 h and also at the subharmonics at about 12 and 8 h, which points to a strong influence of the circadian rhythm. There are further indications for other influences from infra- and ultradian rhythms and possibly from changes of the anticonvulsant medication. On the other hand, important aspects of the epileptic process that typically act on time scales from seconds up to a few hours were reported to contribute to a lesser extent to the temporal variability of the network characteristics. These findings are of importance for future seizure-prediction studies based on network characteristics as well as for studies that aim at shedding further light into the complex interactions between physiological and pathophysiological activities in large-scale brain networks.

8 Conclusions and outlook

We summarized developments of bivariate time-series-analyses techniques that aim at assessing strength and direction of interactions as well as methodologies for deriving and characterizing evolving networks from empirical time series. At the example of evolving epileptic brain networks, we discussed the progress that has been made in capturing and improving our understanding of brain dynamics that varies on time scales ranging from seconds to years. In a work of this scope, it is inevitable that some contributions may be over- or underemphasized, depending upon the points to be made in the text.

It is quite difficult to decide which of all the approaches presented here is the best, given problems for which there are by now no satisfactory and commonly accepted solutions. It is therefore advisable to consider the different characteristics as tentative indices of interacting brain systems and to carefully apply various methodologies that are sensitive to different aspects of time-varying brain dynamics.

Capturing time-varying brain dynamics remains a demanding issue, given the difficulties associated with unequivocally deriving causal relationships from empirical data together with the challenges associated with mapping between multichannel time-series data and complex networks as well as their robust classification. We are confident though that further developments will allow for an improved inference and characterization of time-varying physiological and pathophysiological brain dynamics.

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Authors' contribution

All authors have written the paper and have given final approval for its publication.

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