# The importance of edges in complex networks

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# Abstract

*The sun, the climate, world politics, the stock market, or the human brain, complex networked systems are deeply intertwined in the world we live in. Their dynamics, which include unexpected and catastrophic extreme events, can have tremendous impact on a single human or man-kind as a whole. Hence, studying these systems' dynamical phenomena as well as their properties is essential to improve our knowledge about them. Under the key premise that a complex system can be divided into interacting elementary units, the network ansatz poses a very useful and decisive approach to characterise the system. Associating network vertices with elementary units and network edges with interactions between them, this ansatz yields vast applicability to various natural or man-made systems. Even for those cases, where interactions have no structural correlate or cannot be inferred directly, utilizing time-series-analysis techniques to investigate the units' dynamics allows to characterize properties of interactions, like their strength, direction or even coupling functions, ultimately constituting a time-evolving functional network. Graph theory assesses networks as mathematical structures and provides a multitude of concepts and metrics to assess network characteristics from a global scale, viewing the network as a whole, over an intermediate scale, focusing on substructures in it, to a local scale, inspecting properties of single vertices and edges. Knowledge gained in this way about the properties of the network can then be related to properties of the investigated system and aid to understand its complex emergent global dynamics. While in many ways it is the intricate interplay of interactions between the systems' elements that dictates its properties and dynamics, the edges of networks and their properties have been vastly overlooked. Therefore in this thesis, we embarked on a more edge-centric approach to investigate complex systems utilizing the network ansatz. We developed novel concepts, advanced local network metrics, proposed novel edge-centric metrics and introduced network decomposition algorithms, set out to improve our understanding of real-world systems and their complex dynamics. We demonstrated the applicability and added value of these concepts and metrics, and gained vital insights about archetypical network topologies, spreading phenomena, as well as critical transitions and their entailed extreme events. On the prime example of a complex dynamical system, able to self-generate extreme events, the human epileptic brain, we elucidated vital aspects of network mechanisms involved in the generation of epileptic seizures, e.g. in revealing specific tipping elements and tipping subnetworks. This can ultimately aid in developing more refined approaches to characterize, predict and possibly even mitigate extreme events, such as epileptic seizures. We further revealed limitations of the network ansatz, and how this approach can aid in tackling fundamental challenges encountered especially when studying such real-world systems as the brain, included sampling issues and influences of endogenous and external driving forces. Employing the network ansatz and focusing on the intricate interplay of a complex networked system's interactions, provided considerable advances in understanding these systems and their dynamical phenomena, while also paving the way for future research by displaying the immense potential the network ansatz – and especially the study of important edges – can hold.*

# Contents

In the following, the journal articles included in this cumulative thesis are listed as well as how their authors contributed to them:

- **Chapter II: T. Bröhl and K. Lehnertz. A straightforward edge centrality concept derived from generalizing degree and strength. Sci. Rep. 12, 4407 (2022). DOI:** `https://doi.org/10.1038/s41598-022-08254-5`
    - Timo Bröhl performed the research underlying the manuscript.
    - Klaus Lehnertz supervised the research.
    - All authors conceived the research project and wrote the manuscript.
- **Chapter III: T. Bröhl and K. Lehnertz. A perturbation-based approach to identifying potentially superfluous network constituents. Chaos 33(6), 063119 (2023). DOI:** `https://doi.org/10.1063/5.0152030`
    - Timo Bröhl performed the research underlying the manuscript.
    - Klaus Lehnertz supervised the research.
    - All authors conceived the research project and wrote the manuscript.
- **Chapter IV: T. Bröhl, R. von Wrede and K. Lehnertz. Impact of biological rhythms on the importance hierarchy of constituents in time-dependent functional brain networks. Front. Netw. Physiol. 3, 1237004 (2023). DOI:** `https://doi.org/10.3389/fnetp.2023.1237004`
    - Timo Bröhl performed the research underlying the manuscript.
    - Klaus Lehnertz and Randi von Wrede supervised the research.
    - All authors conceived the research project and wrote the manuscript.
- **Chapter V: T. Bröhl and K. Lehnertz. Identifying edges that facilitate the generation of extreme events in networked dynamical systems. Chaos 30(7), 073113 (2020). DOI:** `https://doi.org/10.1063/5.0002743`
    - Timo Bröhl performed the research underlying the manuscript.
    - Klaus Lehnertz supervised the research.
    - All authors conceived the research project and wrote the manuscript.
- **Chapter VI: R. Fruengel, T. Bröhl, T. Rings and K. Lehnertz. Reconfiguration of human evolving large-scale epileptic brain networks prior to seizures: an evaluation with node centralities. Sci. Rep. 10, 21921 (2020). DOI:** `https://doi.org/10.1038/s41598-020-78899-7`
    - Rieke Fruengel, Timo Bröhl and Thorsten Rings performed the research underlying the manuscript.
    - Klaus Lehnertz supervised the research.
    - All authors conceived the research project and wrote the manuscript.

- **Chapter VII: T. Bröhl and K. Lehnertz. Emergence of a tipping subnetwork during a critical transition in networked systems: A new avenue to extreme events. Phys. Rev. Research 7, 023109 (2025). DOI:** `https://doi.org/10.1103/PhysRevResearch.7.023109`
  - Timo Bröhl performed the research underlying the manuscript.
  - Klaus Lehnertz supervised the research.
  - All authors conceived the research project and wrote the manuscript.
- **Chapter VIII: T. Bröhl, T. Rings, J. Pukropski, R. von Wrede and K. Lehnertz. The time-evolving epileptic brain network: concepts, definitions, accomplishments, perspectives. Front. Netw. Physiol. 3, 1338864 (2024). DOI:** `https://doi.org/10.3389/fnetp.2023.1338864`
  - All authors contributed equally to the review and wrote the manuscript.

In addition, the following articles, produced during the time of my doctoral studies, have strong thematic reference to the contents presented in this manuscript, however are not included in the cumulative thesis.

Reviews:

- T. Bröhl, T. Rings and K. Lehnertz. **From Interactions to Interaction Networks: Time-dependent Functional Networks at the Example of Epilepsy**. Klin. Neurophysiol. 51(03) (2020). DOI: `https://doi.org/10.1055/a-1195-9190`
  - Timo Bröhl, Thorsten Rings and Klaus Lehnertz supervised the review project.
  - All authors conceived the review project and wrote the manuscript.
- K. Lehnertz, T. Bröhl and T. Rings. **The human organism as an integrated interaction network: recent conceptual and methodological challenges**. Front. Physiol. 11, 598694 (2020). DOI: `https://doi.org/10.3389/fphys.2020.598694`
  - Klaus Lehnertz supervised the research project.
  - All authors conceived the research project and wrote the manuscript.
- K. Lehnertz, T. Bröhl and R. von Wrede. **Epileptic-network-based prediction and control of seizures in humans**. Neurobiol. Dis. 181, 106098 (2023). DOI: `https://doi.org/10.1016/j.nbd.2023.106098`
  - Klaus Lehnertz, Timo Bröhl and Randi von Wrede supervised the review project.
  - All authors conceived the review project and wrote the manuscript.

Reasearch on Vagus Nerve Stimulation:

- T. Rings, R. von Wrede, T. Bröhl, S. Schach, C. Helmstaedter and K. Lehnertz. **Impact of transcutaneous auricular vagus nerve stimulation on large-scale functional brain networks: From local to global**. Front. Physiol. 12, 700261 (2020). DOI: `https://doi.org/10.3389/fphys.2021.700261`
  - Timo Bröhl performed the research regarding local network characteristics.
  - Thorsten Rings performed the research regarding global network characteristics.
  - Randi von Wrede, Sophia Schach and Christoph Helmstaedter provided guidance in clinical research and interpretation.
  - Klaus Lehnertz supervised the research project.
  - All authors conceived the research project and wrote the manuscript.

- R. von Wrede, T. Bröhl, T. Rings, J. Pukropski, C. Helmstaedter and K. Lehnertz. **Modifications of functional human brain networks by transcutaneous auricular vagus nerve stimulation: impact of time of day**. Brain Sci. 12(5) (2022). DOI: `https://doi.org/10.3390/brainsci12050546`
  - Timo Bröhl and Thorsten Rings performed the data (pre-)processing and the research regarding network characteristics.
  - Randi von Wrede, Timo Bröhl, Thorsten Rings and Klaus Lehnertz conceptualized the results.
  - Randi von Wrede and Jan Pukropski provided guidance in clinical and neuropsychological research and interpretation.
  - Klaus Lehnertz and Randi von Wrede supervised the research project.
  - All authors conceived the research project and wrote the manuscript.
- R. von Wrede, T. Rings, T. Bröhl, J. Pukropski, S. Schach, C. Helmstaedter and K. Lehnertz. **Transcutaneous auricular vagus nerve stimulation differently modifies functional brain networks of subjects with different epilepsy types**. Front. Hum. Neurosci. 16, 867563 (2022). DOI: `https://doi.org/10.3389/fnhum.2022.867563`
  - Timo Bröhl performed the research regarding local network characteristics.
  - Thorsten Rings performed the research regarding global network characteristics.
  - Randi von Wrede, Timo Bröhl, Thorsten Rings, Christoph Helmstaedter and Klaus Lehnertz conceptualized the results.
  - Randi von Wrede, Jan Pukropski, Sophia Schach and Christoph Helmstaedter provided guidance in clinical research and interpretation.
  - Klaus Lehnertz and Randi von Wrede supervised the research project.
  - All authors conceived the research project and wrote the manuscript.
- H. Lehnertz, T. Bröhl, T. Rings, R. von Wrede and K. Lehnertz. **Modifying functional brain networks in focal epilepsy by manual visceral-osteopathic stimulation of the vagus nerve at the abdomen**. Front. Netw. Physiol. 3, 1205476 (2023). DOI: `https://doi.org/10.3389/fnetp.2023.1205476`
  - Hendrik Lehnertz performed the manual vagus nerve stimulation.
  - Timo Bröhl performed the research regarding local network characteristics.
  - Thorsten Rings performed the research regarding global network characteristics.
  - All authors conceptualized the results.
  - Randi von Wrede provided guidance in clinical research.
  - Klaus Lehnertz and Randi von Wrede supervised the research project.
  - All authors conceived the research project and wrote the manuscript.

Other research:

- K. Lehnertz, T. Rings and T. Bröhl. **Time in brain: how biological rhythms impact on EEG signals and on EEG-derived brain networks**. Front. Netw. Physiol. 1, 755016 (2021). DOI: `https://doi.org/10.3389/fnetp.2021.755016`
  - Thorsten Rings performed the research regarding statistical moments of brain dynamics and temporal changes of interaction properties of brain dynamics.
  - Timo Bröhl performed the research regarding global and local characteristics of evolving brain networks.
  - All authors conceptualized the results.
  - Klaus Lehnertz supervised the research project.
  - All authors conceived the research project and wrote the manuscript.
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  - Timo Bröhl performed the research regarding local network characteristics.
  - All authors conceptualized the results.
  - Klaus Lehnertz supervised the research project.
  - All authors conceived the research project and wrote the manuscript.
- A. Ray, T. Bröhl, A. Mishra, S. Ghosh, D. Ghosh, T. Kapitaniak, S. K. Dana and C. Hens. **Extreme events in a complex network: Interplay between degree distribution and repulsive interaction**. Chaos. 32(12) (2022). DOI: `https://doi.org/10.1063/5.0128743`
  - Arnob Ray performed the research.
  - Timo Bröhl advised on network theoretical aspects.
  - Arindam Mishra, Dibakar Ghosh, Syamal K. Dana and Chittaranjan Hens supervised the research project.
  - All authors conceived the research project and wrote the manuscript.

- M. Potratzki, T. Bröhl, T. Rings and K. Lehnertz. **Synchronization dynamics of phase oscillators on power grid models**. Chaos 34, 043131 (2024). DOI: `https://doi.org/10.1063/5.0197930`
  - Max Potratzki performed the research regarding the power grid models and paradigmatic network models.
  - Timo Bröhl performed the research regarding paradigmatic network models and local network characteristics.
  - Thorsten Rings performed the research regarding global network characteristics.
  - Klaus Lehnertz supervised the research project.
  - All authors conceived the research project and wrote the manuscript.
- M. Badr, T. Bröhl, N. Dissouky, C. Helmstaedter and K. Lehnertz. **Stable yet destabilized: Towards understanding brain network dynamics in psychogenic disorders**. Sci. Rep. - Under Review (2024).
  - Timo Bröhl performed the research regarding global network characteristics and local network characteristics.
  - Mostafa Badr, Timo Bröhl and Klaus Lehnertz conceptualized the result.
  - Mastafa Badr, Nayrin Dissouky and Christoph Helmstaedter provided guidance in clinical research and interpretation.
  - Klaus Lehnertz supervised the research project.
  - All authors conceived the research project and wrote the manuscript.

According to the Doctoral Degree Regulations of the Faculty of Mathematics and Natural Sciences of the University of Bonn (Version 2023) the accepted manuscripts and a manuscript under review for these articles are included in the appendix. Summaries of the respective publications are included as single chapters in this doctoral thesis. Literature citations within the respective summaries are included in the the complete list of literature citations.

# I Introduction

*"We never know how our small activities will affect others through the invisible fabric of our connectedness. In this exquisitely connected world, it's never a question of 'critical mass'. It's always about critical connections."*

– Margaret J. Wheatley (1999). "Leadership and the New Science: Discovering Order in A Chaotic World", p.45, Berret-Koehler Publishers, San Francisco

## A. Motivation

Complex dynamical systems surround us almost everywhere in our day-to-day lives, having vital impact on humanities' existence. Whether man-made or natural, these systems are capable of exhibiting a rich variety of *dynamical phenomena* like travelling waves [1, 2], self-organization [3–5], (de-)synchronization (patterns) [6–8], emergence [9–11], bifurcations [12–15], criticality and multistability [16–18], chimera states [19–21], (critical) phase transitions, and extreme events [22, 23], living on various spatial and temporal scales. They can have large effects on humans individually, humanity as a whole and the world that we live in. Hence, it is vital and in our best interest to understand and predict these *dynamics* and possibly control the systems to tackle a multitude of today's most pronounced and global challenges, including climate change, pandemic spreading, financial crises, and wars. While the desire and the strive to understand such complex and interwoven systems is a challenging task, reductionism and abstraction has allowed great advances in tackling these challenges from a physics point-of-view.

Presuming that such spatially extend complex dynamical systems can be divided into smaller and possibly elementary subsystems, quite often the interplay of these single elements dynamics' can lead to an *emergent* global dynamic.

Comprehending emergence in complex dynamical systems allowed us to understand many complex phenomena in physics like the appearance of magnetism from the macroscopic behaviour of millions of spins or how the ensemble of quantum particles can lead to phenomena such as Bose-Einstein condensation or to material properties such as superconductivity.

Further examples of such complex dynamical systems are many-particle systems found in various different fields of physics, such as electrons in metals in condensed matter physics [24], ideal gas in thermodynamics [25], polymers in material sciences [26–28] or molecular clouds in astrophysics [29]. However, the global linear or non-linear dynamic of such a system is not trivially deducible from properties and dynamics of the elementary subsystems [30, 31].

The key and success in describing these systems and their interesting respective phenomena lies in focusing on the interactions between their constituting elements. The laws of thermodynamics, understood through the microscopic theory called *statistical mechanics*, allowed Ludwig Boltzmann to introduce a framework that connects the (dynamical) behaviour of individual microscopic particles or units to the macroscopic (ensemble) properties of matter. In this sense, the concept of *entropy $S$* provides a formal description of the relation between the microscopic and macroscopic scales of a complex dynamical system. Hence, the definition of entropy by Boltzmann poses a fundamental building block of statistical mechanics:

$$S = k_B \ln \Omega$$

with $k_B$ being the Boltzmann constant, and $\Omega$ being the number of possible microscopic states corresponding to the macroscopic state of the system.

The discovery that statistical mechanics allows to derive certain thermodynamic properties from the behaviour and properties of microscopic particles, was revolutionary in the sense that it allowed to provide deeper insights in how macroscopic phenomena in complex dynamical system arise from the microscopic interactions of the system's constituents.

The principles of statistical mechanics, developed to describe systems of particles, can be extended to formulate the statistical mechanics of networks [32], allowing to relate the emergence of structures and (dynamical) phenomena on a macroscopic scale of networks to the microscopic properties of the network constituents. This postulates the basis of the *network ansatz*, describing a complex dynamical systems as an (evolving) network consisting of interacting units.

Much like in classical statistical mechanics, the physics aspect lies in the characterisation of the systems' states, e.g. via examining energy dependencies affecting probabilities to encounter specific states, or restrictions and exclusion of specific states. Each state can be associated with a network, and hence, the state-space can be represented as a set of networks. Grasping the dynamics of complex dynamical systems requires to identify limitations on the respective network(s). As network dynamics often cover sizable phase-space volumes, approaching the system from a statistical mechanics point-of-view is quite practical and possibly advantageous. The phase-space of networks can then be conceptualized as the set of all possible networks (equivalent to all possible values of position in a mechanical system) that describe the complex dynamical system and how these networks transition into each other (equivalent to the momentum variables in a mechanical system). These advances brought forth unexpected relations to different fields of physics, e.g, in condensed matter physics such as percolation or Bose-Einstein condensation.

Further, and due to the nature of interacting subsystems in many real-world complex dynamical systems, the network ansatz poses a great and recordedly successful approach to study a vast variety of different systems found in diverse (interdisciplinary) areas of science including physics [33–41], geosciences [42], climate sciences [43, 44], computer sciences [45], biology [46–49], social sciences [50–54], and neurosciences [55–66].

With the network approach, a system's (elementary) units are represented as network vertices and interactions between units are represented as network edges. Such networks are often described as *complex networks* due to the complexity of their non-trivial topological make-up, which is also refereed to as coupling structure, and describes how vertices are connected to each other. For complex networks, the coupling structure can be deemed fairly different to regular structures such as lattices or rings [33–36] and also different to topologies on the opposite end of this spectrum, being random structures [67–70]. The relationship between a system's emergent collective dynamic, its subsystems individual dynamics, coupling structure and of course the system's full functionality are often-times not comprehensively understood. Different mathematical *network metrics* deduced form *graph theory* [71] allow to characterise various topological and spectral properties of networks and their constituents, which again can be related to properties of the described complex systems. From the network perspective, properties of the dynamics of a complex system are reflected in the topological aspects of an *interaction network*, for which, and in contrast to the *structural network*, an edge represents an interaction that does not necessarily correlate to a physical connection. Hence, edges in a network might either represent (physical) couplings or characteristics of an interaction between coupled elementary units, with the latter often being derived from the temporal evolution of suitable observables of the units' dynamics.

As such complex dynamical systems may evolve in time, due to exogenous or endogenous factors, it is also to be considered that the respective complex networks should evolve in time, altering the coupling structure, the properties of network constituents and possibly even the composition of the network as a whole. Such *time-evolving networks* [72], respectively represented via *snapshot networks* in time, potentially allow a more accurate description and investigation of complex dynamical systems. However, comparing (snapshot) networks in order to track meaningful and significant changes and alterations within the time-evolving network, is a challenging task, as yet there is no commonly accepted and robust way to compare networks [73–78]. Yet again, utilizing network metrics to describe network properties from the global to the local scale allows to circumvent this issue when interpreted in a suitable context and in unison [79].

The network ansatz has been largely utilized focusing on either global network properties or the networks' vertices, in interaction as well as in structural (evolving) networks, predominantly deeming vertices as the prominent and defining network constituents. However, in many ways, it is the intricate interconnectedness of systems' (elementary) units, as well as how this interconnectedness changes, that, to a great extend, shapes the emergent dynamical properties and behaviours of complex dynamical systems. Whether it is the neural pathways in our brains, the intricate web of interactions in ecological communities, the digital interconnections in social media networks, or the complex interplay of tipping elements in the climate, these kinds of connections serve as conduits for information, influence, and change, decisively shaping the range and exhibition of possible dynamics of the respective complex system. Simplified and figuratively speaking, observing a clogged intersection in a busy city road network might give us insights into the occurring dynamical phenomena of traffic jams, but it may be the too narrow or faulty roads or even a car accident on one of these roads, which lead to the traffic jam.

Hence, gaining deeper insights about the role and essence of interactions between units in a complex dynamical system is essential for unraveling the conundrums of emergent phenomena, predicting system-wide dynamical behaviours, and designing interventions to alter such behaviours, largely associated with real-world challenges. Research of the last decades [33, 36, 80–84] has already revealed that properties of pairwise interactions, mainly their strength, direction and functional forms, not only hold intricate information about a systems characteristics, such as resilience [40, 85–87], stability and adaptability [88] but that the temporal evolution of these interaction properties can directly influence the systems' characteristics [36, 72, 89].

At the heart of this dissertation lies the exploration of how interactions in complex dynamical system, represented by edges in complex networks, drive the many diverse dynamics a (spatially-extended) complex dynamical system can exhibit. By dissecting the intricate interplay between the systems' (elementary) subsystems (vertices), conveyed by their interactions (edges), we aim to uncover the underlying mechanisms that govern the (collective) dynamical behaviour of diverse systems, man-made and observed in nature – ranging from social structures to complex biological systems such as the human brain. By deciphering the importance and the roles of edges, as well as their potential superfluousness in complex networks, we can enhance our understanding of (critical and often disastrous) phenomena such as (de-)synchronization, the spread of disease or information and the generation and occurrence of extreme events in many natural systems (such as market crashes, extreme weather events, power blackouts, epileptic seizures etc.). Expanding our knowledge about such dynamical processes – by focusing on network edges – can inform the development of strategies for network optimization, targeted interventions, and counteracting network alterations which can possibly be translated to application of real-world actions aiming to understand, predict or even control the many diverse dynamical systems.

This first chapter is organized as the following: We begin by introducing the mathematical and physical basis of networks as well as how to characterise them. As the characterisation of networks and their properties allows the proposition of network models, we subsequently discuss paradigmatic network models, which respectively, or in combinations of such, are found in nature. Estimating networks for complex dynamical systems in nature is, however, neither an easy task nor is there a commonly accepted and generally applicable approach to do so. We elaborate on the differences of an underlying structural network of a *networked dynamical system* and the concept of a respective functional network, with the letter aiming to grasp the essence of the system's interactions and their properties, especially for those cases where knowledge about the relevant structural connections in the complex dynamical system is insufficient. We discuss how to infer such *functional interaction networks* from empirical (time series) data and further take into account that many complex dynamical systems evolve in time, which deems a description of such systems via a static network insufficient. Consequently we advance to the description of time-evolving networks, and how to infer time-evolving networks from data, as well as how to assess changes in evolving networks via the temporal evolution of network properties.

The description of complex dynamical systems via time-evolving networks provides great potential for a more in-depth investigation of interesting and highly relevant dynamical phenomena such as critical transitions, that may culminate in extreme events. We introduce a frequently proposed definition of an extreme event from a physics perspective, and highlight the relevance of studying critical transitions and extreme events due to their occurrence in many different complex dynamical systems in nature, and their often disastrous consequences, ranging from a local scale of single individuals to a global scale of the majority of the world's population. We elaborate on the interest and possible approaches to predict, understand and control extreme events, utilizing the network approach. We introduce the different systems, investigated throughout this thesis, that are either capable or known to exhibit relevant and interesting dynamical behaviours – focusing especially on extreme events – or pose suitable real-world networks, which allow to investigate the applicability and suitability of different approaches and metrics presented in the following chapters of this thesis. Hereby we largely focus on the interactions in the respective network and aiming to gain deeper insights in the dynamic behaviour of the respective systems. Lastly we outline the structure of this thesis throughout these different chapters.

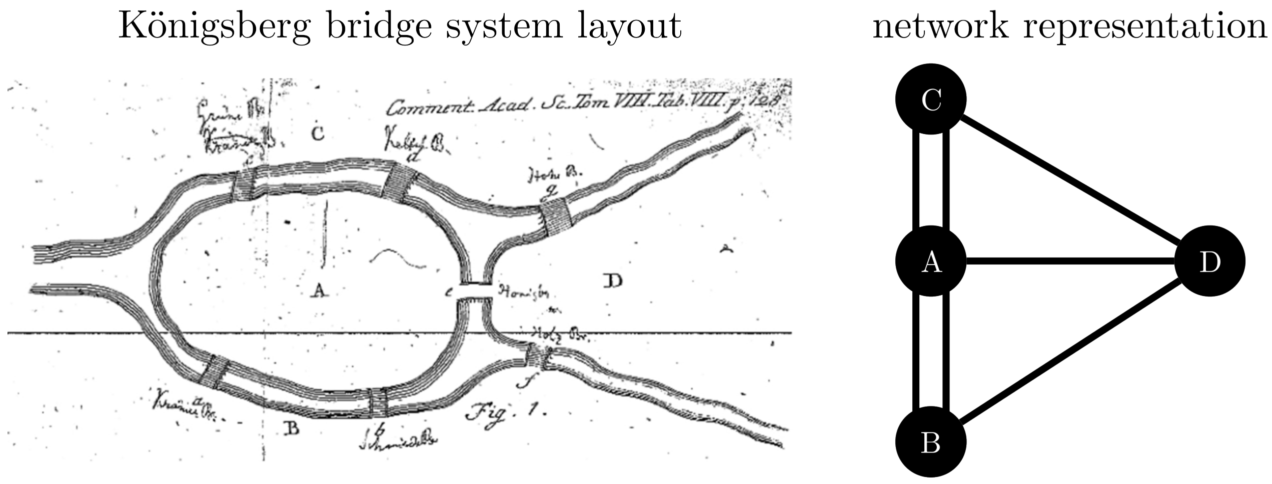
## B. Networks

In mathematics, a network is defined as a collection of *vertices* (or *nodes*) connected by *edges* (or *links*). Formally, a network can be represented by a graph $G = (\mathcal{V}, \mathcal{E})$ consisting of a set of vertices $\mathcal{V} = \{v_1, v_2, \ldots, v_\mathrm{V}\}$, containing all $\mathrm{V} = |\mathcal{V}|$ vertices in the network, and a set of edges $\mathcal{E} = \{e_1, e_2, \ldots, e_\mathrm{E}\}$, containing all $\mathrm{E} = |\mathcal{E}|$ pairs of vertices connected by an edge. The terms graph and network are often used interchangeably, having been associated with each other, more than half a century ago [67, 68]. Nowadays the two terms generally refer to the same concept with only nuanced differences depending on the field of study [90] while the fundamental idea of vertices connected by edges remains consistent between graphs and networks.

A network can be considered *binary*, meaning an edge either exists between two vertices or it does not, or *weighted*, meaning that with every edge a certain additional information is associated - often labeled as the *edge weight*. An edge weight can represent a variety of properties related to the connection between two vertices and is very individual for the respective network. Hence, the properties represented by edge weights can range from simple, e.g., physical connections such as the length of a street, railway connection, or the distance/duration of a flight between two locations (vertices), to abstract connections such as the strength of relationships between individuals or spreading probabilities (of information or viruses) between organisms or larger more abstract structures (countries or continents), to the strength of complex connections between coupled elementary units of a larger complex system (e.g., the interaction strength between power plants and consumers in a power gird or the interaction strength between different parts of a brain network). Mathematically, a binary network of V vertices may be represented via its *(vertex) adjacency matrix* $\mathbf{A} \in \{0,1\}^{\mathrm{V}\times\mathrm{V}}$, with $A_{ij} = a_l = 1$ if there is an edge $l$ connecting vertices $i$ and $j$ and $A_{ij} = a_l = 0$ otherwise. Analogously, a weighted network of V vertices can be described by its *weight matrix* $\mathbf{W} \in \mathbb{R}_+^{\mathrm{V}\times\mathrm{V}}$, with $W_{ij} = w_l$ equalling the weight associated with the edge $l$ connecting vertices $i$ and $j$, and $W_{ij} = 0$ if the edge does not exist or has no weight. While these matrix representations of networks are most commonly used, it is also to be noted, that another viewpoint allows the definition of an *edge adjacency matrix* $\mathbf{A}^{(\mathrm{e})} \in \{0,1\}^{\mathrm{E}\times\mathrm{E}}$, with $A_{lm}^{(\mathrm{e})} = 1$ if two edges $l$ and $m$ are adjacent (connected to a same vertex) and $A_{lm}^{(\mathrm{e})} = 0$ otherwise, in case of a binary network. Analogously the definition of a *weighted edge adjacency matrix* is $\mathbf{W}^{(\mathrm{e})} \in \mathbb{R}_+^{\mathrm{E}\times\mathrm{E}}$, with $W_{lm}^{(\mathrm{e})}$ varying in definition, but most commonly being assigned the average of the weights associated with edges $l$ and $m$.

The interaction between two vertices in a network can either be *undirected* (a direction of interaction is not relevant), *directed* (one of the two vertices can be considered the driver while the other is considered the receiver) or *bidirectional* (the vertices drive each other and receive from each other). While concepts of direction and multi-edge networks may allow a more accurate detailed description of certain complex systems in nature [83, 91–94], their application and resulting interpretations become adherently more complex. In this thesis, we only consider binary or weighted, undirected ($\mathbf{A}$, $\mathbf{A}^{(e)}$, $\mathbf{W}$ and $\mathbf{W}^{(e)}$ are symmetric) and connected networks, excluding so-called self-loops – a vertex connected to itself by an edge ($A_{ii} := 0$ and $W_{ii} := 0$ for $i \in \{1, \ldots, \mathrm{V}\}$, $A^{(\mathrm{e})}_{ll} := 0$ and $W^{(\mathrm{e})}_{ll} := 0$ for $l \in \{1, \ldots, \mathrm{E}\}$).

One of the earliest recorded introduction of network theory is the famous mathematician and physicist Leonhard Euler's approach to tackling the problem of "The Seven Bridges of Königsberg" in 1741 [95]. Königsberg (now Kaliningrad, Russia) was divided into four landmasses by the Pregel River. Two islands (Kneiphof and Lomse) as well as North and South Bank of the city. These landmasses were connected by seven bridges as shown in maps of the city (cf. Fig. 1).


Königsberg bridge system layout

network representation

FIG. 1. Left: Original schematic depiction of the bridge layout in Königsberg by Leonhard Euler [95]. The landmasses are labelled A,B,C and D. Right: Network representation of the bridges in Königsberg connecting the four landmasses represented as vertices A,B,C and D (Kneiphof, the South Bank, the North Bank and Lomse). Vertices A,B and C have multi-edges. In total, three respective edges lie on the vertices B, C and D, while five edges lie on vertex A.

The challenge was – starting from an arbitrary position in Königsberg – to find a path through the city that would cross each of the seven bridges exactly once. Euler simplified and abstracted the problem by associating the landmasses with vertices and bridges with edges and showed mathematically, that in order for the described path to exist, each of the vertices has to have an even number of edges connected to it. In the historical Königsberg, this condition was not given as on each of the landmasses an odd number of bridges could be found, allowing Euler to conclude that the desired path did not exist. As a result of the destruction of two of the seven bridges in World War I, the network was modified in such a way that the condition was then fulfilled, allowing to traverse each of the then five bridges exactly once to return to an arbitrary starting point on one of the landmasses. Euler's solution not only showed the power of abstraction of such complex problems but further laid the foundation for the formal study of networks and their properties.

In the following century (19th century), the physicists Gustav Kirchhoff further advanced and significantly contributed to the field of network theory, publishing his fundamental laws for electrical networks in 1845, known as Kirchhoff's circuit laws [96]. In the 20th century, mathematician and electrical engineer Claude Shannon did seminal work in information theory, introducing fundamental concepts such as information entropy [97]. His theories held vital implications for the design and analysis of communication networks, such as telephone networks, data networks, and ultimately the internet. Further, it indirectly influenced the study of network topology, later inspiring researchers to explore the properties of networks, such as robustness and resilience [86, 98, 99].

### 1. characterising networks

Nowadays a multitude of network metrics allow to assess different topological and spectral network properties, and thus aid to characterise networks from a *global* to a *local* scale (cf. Fig. 2). While topological properties include local and global structural aspects of the network, spectral properties are derived from a network adjacency, weight, or *Laplacian matrix* $\boldsymbol{\mathcal{L}}$ (with $\mathcal{L}_{ij} = \sum_i^{\mathrm{V}} A_{ij}\delta_{ij} - A_{ij}$ for binary networks, resp. $\mathcal{L}_{ij} = \sum_i^{\mathrm{V}} W_{ij}\delta_{ij} - W_{ij}$ for weighted networks, $\delta_{ij}$ representing the Kronecker delta), providing insights into the global network dynamics and characteristics of the network. For instance, *eigenvalues* and *eigenvectors* of matrix representations of the network can provide information about the networks connectivity [100] and robustness [101], however, may also be utilized for community detection [102] or studying network dynamics [103].

The global network metric *synchronizability* [104]

$$S = \frac{\lambda_{\mathrm{V}}}{\lambda_2} \tag{1}$$

is derived from the ratio of the largest $\lambda_V$ and smallest non-vanishing eigenvalue $\lambda_2$ of the Laplacian matrix $\boldsymbol{\mathcal{L}}$, and describes the stability of a fully synchronized state of a network of coupled dynamical units. It further describes the capacity to achieve and maintain such a synchronized state despite heterogeneity in the dynamics of its units [105–107]. Depending on the dynamics of the units, a small synchronizability either indicates that the network's capability to exhibit a synchronized state is limited to begin with (independent of the coupling strength between the units), or indicates the network's high capability of achieving and maintaining a synchronized state among its units.

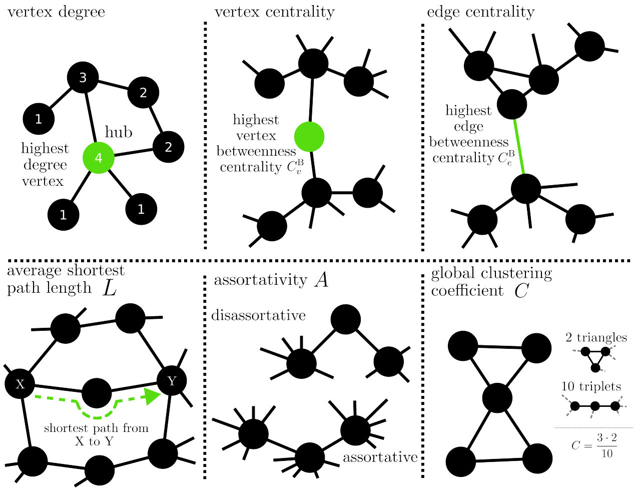


FIG. 2. Schematic depiction of exemplary local (top) and global (bottom) network metrics. Adapted from Chapter VIII.

Global network metrics like the *average shortest path length* $L$ [108] and a network's *(pseudo) diameter* $K$ [109, 110] utilize the concept of a path in a network [109, 111]. A path is generally defined as the set of edges $\mathcal{P}_{ij} \subseteq \mathcal{E}$ which have to be traversed to get from a network constituent (vertex or edge) $i$ to constituent $j$ (or vice-versa). The length of this path $D_{ij} = \sum_l \frac{1}{w_l}$, with $w_l$ corresponding to the weight of edge $e_l \in \mathcal{P}_{ij}$, is thus defined as the sum of the inverse edge weights associated with the edges along this path. In a binary network $D_{ij} = \sum_l \frac{1}{a_l}$, with $a_l$ corresponding to edge $e_l \in \mathcal{P}_{ij}$. If any $a_l$ or $w_l$ associated with $e_l \in \mathcal{P}_{ij}$ is zero, the path does not exist. Consequently, the *shortest path length* (also referred to as *distance*) $d_{ij} = \min D_{ij}$ between two constituents $i$ and $j$ in a network corresponds to the path $\mathcal{P}_{i,j}$ for which $D_{ij}$ is minium. Therefore, the average shortest path length is defined as

$$L = \frac{1}{\mathrm{V}(\mathrm{V}-1)} \sum_{i,j}^{\mathrm{V}} d_{ij}, \tag{2}$$

and the diameter of a network

$$K = \max\, d_{ij} \tag{3}$$

is defined as the length of the longest of all shortest paths between all possible pairs of vertices $i$ and $j$. Both of these metrics, in their way, assess a network's functional integration, which can be used to describe the information flow in a network [112]. A small $L$ and $K$ indicate short ways of interaction and therefore a fast transport of information [108].

The *global clustering coefficient* $C$ [35, 113] utilizes a local structural aspect in a network: the number of neighbours (adjacent vertices) each vertex has, which is generally called the *degree* $\mathcal{C}_{\mathrm{v}}^{\mathrm{D}}$ of a vertex, with $\mathcal{C}_{\mathrm{v}}^{\mathrm{D}}(i) = \sum_{j}^{\mathrm{V}} A_{ij}$ being the degree of vertex $i$ [114]. The global clustering coefficient is generally defined as the ratio of the number of triangles to the number of connected triples in a binary network (cf. Fig. 3):

$$C = 3\frac{\text{number of triangles}}{\text{number of triples}}. \tag{4}$$

In case of weighted networks, and assuming the weights to be normalized, i.e., $0 \leq W_{ij} \leq 1$, Eq. 4 extents to:

$$C = \frac{\mathrm{Tr}\mathbf{W}^3}{\sum_{i,j}^{\mathrm{V}} [\mathbf{W}^2]_{ij}} \tag{5}$$

The global clustering coefficient assesses the functional segregation of a network, which can be used to describe the extent to which vertices in a network cluster together.

*Assortativity* $A$ [115, 116] of a network assesses the tendency of vertices to be connected, if these vertices share a (dis-)similar feature. Commonly this feature is the degree of the vertices, with the assortativity therefore quantifying the degree-degree correlation in a network:

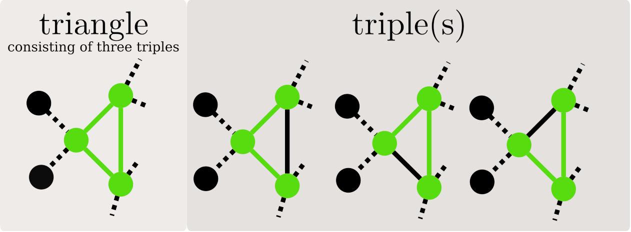


FIG. 3. Exemplary triangle (left) consisting of three triples (right) in an arbitrary network. Vertices and edges constituting the respective triangle and triples are depicted in green.

$$A = \frac{\sum_{xy} xy(e_{xy} - p_x p_y)}{\sigma_p^2}, \tag{6}$$

with $x$ and $y$ being the degree of two connected vertices, $e_{xy}$ being the fraction of edges that connect vertices with degree $x$ and $y$, $p_z$ being the probability that a randomly chosen vertex has degree $z$, and $\sigma_p^2$ being the variance of the degree distribution. A positive assortativity ($A > 0$) indicates that high-degree vertices are connected to other high-degree vertices while low-degree vertices are connected to other low-degree vertices. This often results in so-called assortative mixing and the formation of a hierarchical or degree-based community structure [115, 117–119]. These large and highly connected substructures or communities (hubs or groups of hubs) can influence the propagation of information in the network and contribute to a network's robustness [120] and resilience [121]. It is observed that such assortative networks are much harder to synchronize than less assortative or even disassortative networks [122, 123]. A negative assortativity ($A < 0$) suggests that the network is disassortative and that vertices with high-degree are connected to low-degree vertices and vice versa, with the network showing a more homogeneous degree distribution and the lack of stronger hierarchical or community structures. Correspondingly $A = 0$ suggest that the network is non-assortative network.

The detection and characterisation of substructures, such as *communities*, *motifs*, *cores*, *shells* and *webs* aims to describe a network on mesoscopic scales [124–127]. Communities, which are also referred to as clusters or modules, most commonly describe a set of vertices in a network, which are more densely connected to each other than to other vertices in the network, hence distinguishing the community from the rest of a network based on strong interconnections or other similarities among communities [128]. Motifs, most commonly refer to recurring (small) substructures in a network [129, 130]. They can aid in uncovering common patterns in a network [131, 132], providing insights into the network's structure-function relationships [36] and dynamical behaviour [133, 134]. Similarly, network decompositions allow to break down complex networks into smaller substructures, based on different aspects of the network's structure and organization. Decomposition techniques, such as the *k-core* or *k-shell decompositions* [135–138], allow to reveal hierarchical structures and provide insights in the organization of vertices based on their degree (or other constituent-specific properties), potentially identifying central or influential or key substructures in a network. As part of this thesis, we will also introduce the so-called *web-decomposition*, which, adapted from the $k$-core/shell decomposition, allows to reveal a bottom-up hierarchy of sets of edges, based on edge-specific properties, that form substructures (*webs*) in the network. We show that these webs can aid in identifying precursor structures of extreme events in networked dynamical systems [139].

Local network metrics are employed with the aim to characterise properties of single network constituents (vertices or edges). Such characterisations can generally be achieved with the concept of *centrality* [140]. Centrality metrics quantify the importance, or influence, or role of constituents in a network, generally estimated based on certain aspects of their structural or functional embedding in the larger network. Centrality metrics can hence provide valuable insights regarding the role of network constituents for information flow and a network's dynamics. The most basic centrality metric is the degree of vertex $i$, as already introduced prior:

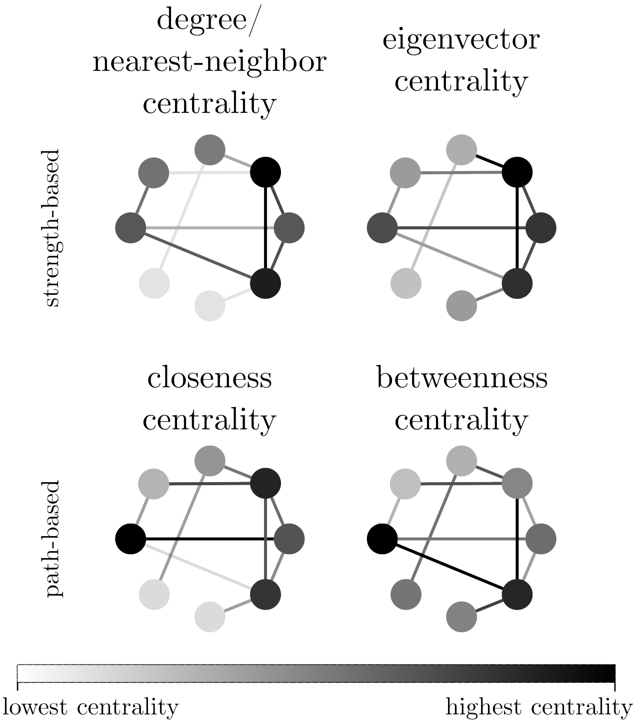


FIG. 4. Exemplary depiction of a (binary) random network with its respective constituents' centrality values assessed via different concepts. Centrality values are colour-coded: the darker the colour of the respective constituent the higher its centrality value. The centrality metrics are separated conceptually (top row: strength-based metrics, bottom row: path-based metrics).

$$\mathcal{C}^{\mathrm{D}}_{\mathrm{V}}(i) = \sum_{j}^{\mathrm{V}} A_{ij}, \tag{7}$$

which, in case of a weighted network, can be extended to the *strength* of vertex $i$:

$$\mathcal{C}_{\mathrm{v}}^{\mathrm{S}}(i) = \sum_{j}^{\mathrm{V}} W_{ij}. \tag{8}$$

Vertices with a high degree or strength are deemed to be (locally) stronger interconnected within a network, and may potentially play central roles in the propagation of information in the network [141, 142].

*Vertex eigenvector centrality* $\mathcal{C}_{\mathrm{v}}^{\mathrm{E}}$ [143] follows the general idea of a vertex' degree or strength having vital impact for its role in the network. It deems a vertex important if its adjacent vertices are important as well. The resulting gradual decrease in the impact of a vertex' neighbourhood results from the recursive definition of

$$\mathcal{C}_{\mathrm{v}}^{\mathrm{E}}(i) = \frac{1}{\lambda} \sum_{j}^{\mathrm{V}} M_{ij} \mathcal{C}_{\mathrm{v}}^{\mathrm{E}}(j) \tag{9}$$

with $\lambda$ corresponding to the largest eigenvalue and eigenvector $\mathbf{x}$ of $\mathbf{M}$ with $\mathbf{M}\mathbf{x} = \lambda \mathbf{x}$, $\mathbf{M} = \mathbf{A}$ in case of a binary network and $\mathbf{M} = \mathbf{W}$ in case of a weighted network. By now, there are several variations and extensions of eigenvector centrality such as EigenTrust [144], Katz centrality [145] and PageRank [146], the latter famously known for being part of the Google search engine algorithm.

Besides strength-based centrality metrics, path-based centrality metrics have shown successful applications in different scientific fields. *Vertex closeness centrality* [114] utilizes the concept of a path and the length of paths in a network. A vertex is considered the more important if its distance to all other vertices is small, leading to the definition of

$$\mathcal{C}_{\mathrm{v}}^{\mathrm{C}}(i) = \frac{\mathrm{V} - 1}{\sum_{j}^{\mathrm{V}} d_{ij}} \tag{10}$$

for vertex $i$ in the network.

Another path-based centrality metric is *vertex betweenness centrality* $\mathcal{C}_{\mathrm{v}}^{\mathrm{B}}$ [108, 124, 147–149], for which a vertex is considered the more important, the more commonly this constituent is part of the shortest path between every possible pair of vertices. Hence, it does not consider the distance between two vertices in a direct manner, but the number of shortest paths between them. It is defined as

$$\mathcal{C}_{\mathrm{v}}^{\mathrm{B}}(i) = \frac{2}{(\mathrm{V}-1)(\mathrm{V}-2)} \sum_{i \neq j \neq k}^{\mathrm{V}} \frac{q_{jk}(i)}{G_{jk}} \tag{11}$$

for vertex $i$ with $q_{jk}(i)$ denoting the number of shortest paths between vertices $j$ and $k$ traversing vertex $i$ and $Q_{jk}$ denoting the total number shortest path between vertices $j$ and $k$. Vertices with high betweenness vertex centrality can be considered to serve as bridges, intermediaries or bottlenecks in a network, greatly influencing the flow of information between different parts of it [150–152].

Noticeably, the above mentioned centrality metrics focus on vertices, as surprisingly few centrality metrics have been defined to characterise the role of individual edges. A fact that only changed in the recent decade, with the focus shifting on approaches to achieve an improved characterisation of importance of edges, especially in interaction networks, with the aim to deepen the understanding of and aid the control of such networks [153].

The *edge betweenness centrality* $\mathcal{C}_{\mathrm{e}}^{\mathrm{B}}(l)$ [124] was one of the first edge centrality metrics and is analogously defined to vertex betweenness centrality, with

$$\mathcal{C}_{\mathrm{e}}^{\mathrm{B}}(l) = \frac{2}{\mathrm{V}(\mathrm{V}-1)} \sum_{j \neq k}^{\mathrm{V}} \frac{q_{jk}(l)}{G_{jk}} \tag{12}$$

for edge $l$ with $q_{jk}(l)$ denoting the number of shortest paths between vertices $j$ and $k$ traversing edge $l$ and $Q_{jk}$ denoting the total number of shortest paths between vertices $j$ and $k$. Hence, an edge is the more important the more shortest paths in the network include it. Yet, it is apparent that betweenness edge centrality is based on vertex specific properties, being the shortest paths between them. Therefore, in prior research to this thesis, we adapted and modified the frequently used metrics of vertex closeness and eigenvector centrality, and introduced *edge closeness centrality* $\mathcal{C}_{\mathrm{e}}^{\mathrm{C}}$ and *edge eigenvector centrality* $\mathcal{C}_{\mathrm{e}}^{\mathrm{E}}$ [127]. In case of edge closeness centrality, edge $l$ is deemed the more important, the shorter the paths that connect this edge to every other reachable edge in the network, yielding

$$\mathcal{C}_{\mathrm{e}}^{\mathrm{C}}(l) = \frac{\mathrm{E}-1}{\sum_m^{\mathrm{E}} d_{lm}}. \tag{13}$$

In case of edge eigenvector centrality, edge $l$ is deemed the more important, the more important its adjacent edges are, yielding

$$\mathcal{C}_{\mathrm{e}}^{\mathrm{E}}(l) = \frac{1}{\lambda}\sum_m^{\mathrm{E}} M_{lm}\mathcal{C}_{\mathrm{e}}^{\mathrm{E}}(m) \tag{14}$$

with $\lambda$ corresponding to the largest eigenvalue and eigenvector $\mathbf{x}$ of $\mathbf{M}$ with $\mathbf{Mx} = \lambda\mathbf{x}$, and $\mathbf{M}$ corresponding to the edge adjacency matrix ($\mathbf{M} = \mathbf{A}^{(\mathrm{e})}$ in case of a binary network and $\mathbf{M} = \mathbf{W}^{(\mathrm{e})}$ in case of weighted network).

As a part of this thesis, we further introduced a novel edge centrality metric, the so-called *nearest-neighbor centrality* $\mathcal{C}^{\mathrm{N}}$, derived from generalizing the concepts degree and strength of a vertex [154]. This metric deems edge $l$ to be more important the larger its weight and the more similar and the higher the strengths of vertices $i$ and $j$ connected by that edge, yielding

$$\mathcal{C}_{\mathrm{e}}^{\mathrm{N}}(l) = \frac{\mathcal{C}_{\mathrm{v}}^{\mathrm{D}}(i) + \mathcal{C}_{\mathrm{v}}^{\mathrm{D}}(j) - 2}{|\mathcal{C}_{\mathrm{v}}^{\mathrm{D}}(i) - \mathcal{C}_{\mathrm{v}}^{\mathrm{D}}(j)| + 1} \tag{15}$$

for binary networks, and

$$\mathcal{C}_{\mathrm{e}}^{\mathrm{N}}(l) = \frac{\mathcal{C}_{\mathrm{v}}^{\mathrm{S}}(i) + \mathcal{C}_{\mathrm{v}}^{\mathrm{S}}(j) - 2w_l}{|\mathcal{C}_{\mathrm{v}}^{\mathrm{S}}(i) - \mathcal{C}_{\mathrm{v}}^{\mathrm{S}}(j)| + 1}. \tag{16}$$

for weighted networks.

It is to be noted, that there is a whole 'periodic table of (vertex) centralities', each highlighting and focusing on different aspects of the network when assessing the integration of constituents in the network (see references in Ref. [155]). Certainly, the similarity (in definition and results) between some centralities is larger than in others, still there can be made a case for each of them to justify their relevance.

The four centrality concepts, presented in this thesis (cf. Fig. 4), can be considered complementary in two different aspects: their general consideration of structural aspects in a network and the structural scale of this consideration. Degree/nearest-neighbor centrality and eigenvector centrality are strength-based centrality concepts primarily depending on the degree or edge weight distribution in the network. Here, degree/nearest-neighbor centrality can be considered a highly local centrality concept, as only directly adjacent constituents (local scale) influence their integration in the network. Opposing to that, eigenvector centrality can be considered a more global centrality concept, as it considers the global scale of the neighbourhood of a constituent, with the influence of constituents gradually decreasing as they are more “distant” (not directly adjacent) to each other. On the other hand, closeness and betweenness centrality focus on the path structures in a network. Here closeness centrality only considers specific shortest paths that traverse the respective constituent (local scale) while betweenness centrality takes into account the amount of all shortest paths in a network with respect to the amount of shortest path traversing the respective constituent (global scale).

Generally, it is notoriously difficult to compare local network characteristics, especially centrality metrics, as the different metrics may yield values in different ranges. Ranking these values [156] allows the aimed for comparison between different metrics and has been successfully employed in different research [157–159]. Such a ranking is mostly realized in an ascending order, with the largest value being associated with the smallest/top rank and the most important element (with respect to a specific metric). Nevertheless, ranking also has its limitations, especially when it comes to assign the ranks based on a very narrow distribution of centrality values. Furthermore, equal centrality values may pose a problem, as the same rank could be assigned multiple times. In other cases, certain centrality values may only vary numerically – a numerical difference only present in several digits after the coma – raising the questions whether the integration of these constituents in the network can truly be considered different (based on the definition of the centrality concept). The centrality concepts employed in this thesis yield rather broad distributions of centrality values and negligible occurrences of multiple same centrality values (especially for weighted networks). Throughout this thesis we hence consider to rank by appearance, disregarding the minor effect of possibly equal or "numerically close" (which is highly relative) centrality values.

Although certain correlations between different centrality concepts are given and to be expected, one centrality metric may deem a network constituent to be vital and important, while another may deem it unimportant [127, 160–164], as exemplarily depicted in Figure 4. Hence, different centrality metrics allow to highlight distinct structural and functional aspects of a constituent's embedding in a network. Further, the vertex and edge centrality metrics, employed in this thesis, yield complementary information about the hierarchical structure of the constituents in a network.

### 2. Paradigmatic network models

The *topology* of a network refers to the specific arrangement or structure that vertices are connected within a network [33, 81]. This is largely defined by *topological properties* such as the network's number of vertices V and number of edges E, the network's path structure and the way constituents in the network tend to cluster together (e.g estimated via global network metrics). A set of certain topological properties allows to define distinct types of topologies.

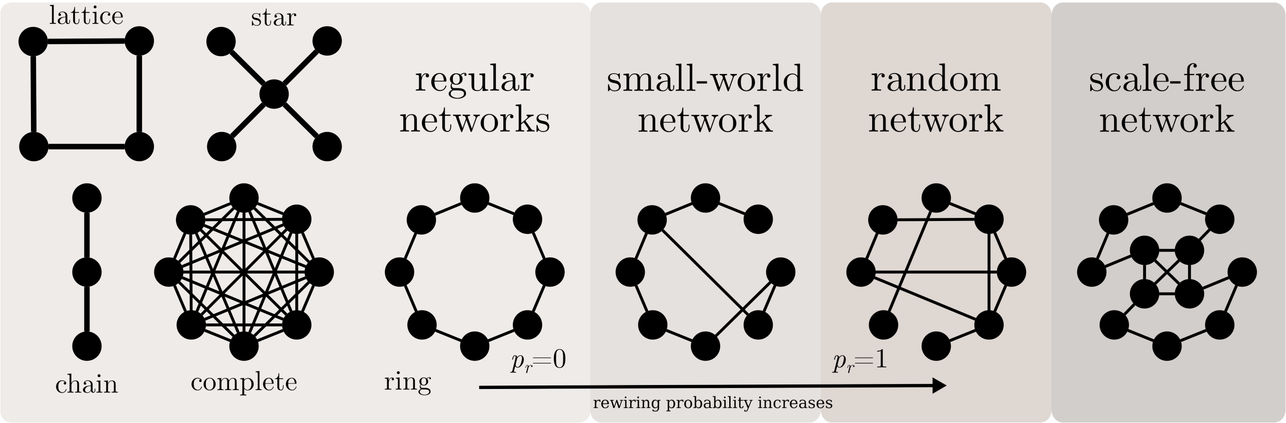


FIG. 5. Exemplary depiction of realizations of paradigmatic network models. Vertices are portrayed as black dots and edges are portrayed as black lines. For purposes of demonstration and highlighting differences between the paradigmatic network models, the depicted networks have a varying number of vertices and edges. Starting from a ring network, the respective small-world network and random network are generated via rewiring of edges with a specific rewiring probability $p_r$ (Watts-Strogatz Model [113]). The scale free network is generated by preferential attachment (Barabási-Albert model [69]) resulting in the formation of a visible highly connected core and a less connected periphery.

The following paradigmatic network models describe such distinct types of topologies (cf. Fig. 5) commonly found in nature and in man-made systems.

- **regular network**: vertices are connected in a regular pattern. This includes very simple structures such as chains, rings, stars or lattices, but also complete networks (in which every vertex is connected to every other). These types of networks are commonly found in man-made systems like road networks [165], computer architecture [166, 167], parallel computation [168] and satellite constellations [169]. Further, they are used for an approximation of spatial-temporal phenomena commonly described by partial differential equations.

- **small-world network**: vertices tend to be clustered, while the average path length between two vertices in the network tends to be short. Being similar to regular networks, like a ring or lattice, small-world networks can be distinguished from such by some few *long-range* connections, that connect two arbitrary vertices in this otherwise regular structure. Hence, small-world networks can be generated e.g. by starting from a regular network and rewiring each edge in this network with a small *rewiring probability* $p_r$ [170]. The specific edge is disconnected from one of its vertices and connected to another randomly chosen vertex [113]. Small-world networks are likely to be the most researched and (critically) discussed paradigmatic network models, as features of small-world networks are reported to be observed in complex brain networks, climate networks, infrastructure networks as well as epidemic and rumour spreading in social networks [56, 171–177].

- **random network**: vertices are randomly connected to each other. In order to generate a random network, similarly to small-world networks, one could start from a regular network and rewire every edge with $p_r$ being large ($p_r = 1$). Though, more commonly, each vertex is connect to any other vertex with some probability $p_e$ [67]. Random networks often serve as baseline or null models when studying the properties and behaviour of other (more complex) networks. Many networks in nature exhibit, at least to some extent, properties comparable to random networks. However, random network models generally do not suffice to describe real-world networks in an exhaustive manner [178].

- **scale-free network**: following a power-law degree distribution, very few vertices have a very high degree, while most vertices have a low degree. This often allows the separation of the network in a *core*, consisting of the few high-degree vertices (also refereed to as *hubs*), and the *periphery*, consisting of the remaining low-degree vertices. The *preferential attachment* model [34], with which newly added vertices preferably attach to existing high-degree vertices, is most commonly used to generate scale-free networks. This type of topology is largely observed in social networks, allowing to prove claims such as from Harvard sociologist, Stanely Milgram, in 1967, that any two people are about five to six handshakes away from each other [179]. This feature is now known as the six-degrees of separation property [180, 181]. Probably by now the most popular scale-free network is the internet [182–184]. Furthermore, studying physical processes taking place on scale-free networks, such as resilience to random damage [98, 185, 186] or epidemic spreading processes [187–190] have shown great success in the last two decades.

Naturally, these paradigmatic network models do not account for every network found in nature, neither do they provide a holistic description for most of them. Employing these models, and combinations of such, to describe complex systems in nature, faces many challenges such as the validation against real-world data. This poses problems and difficulties not only due to complexity and variability of empirical networks but also due to the methods used to estimate networks from data, which encompasses errors in measurements and statistics [176, 177, 191]. Bootstrapping techniques (e.g., time-series surrogates and surrogate networks) can aid in tackling these problems [192–195].

#### 3. Inferring functional interaction networks from empirical (time series) data

Throughout this thesis, we will encounter several complex systems ranging from rather simple social networks, over *networked dynamical systems* (coupled dynamical units such as oscillators), to the complex system brain (see Sec. I D). There is a vast multitude of different methods and approaches to derive networks for these complex (dynamical) systems. Generally, vertices are associated with different subparts of a system, often sampling units or dynamical variables of these units via some sensors. Edges are associated with properties related to interactions between two or more units. Yet, in the majority of investigated systems the underlying equations of motion are not known and the interactions between units of a system cannot be measured directly (e.g., via probing). Therefore, time-analysis-techniques are employed to quantify (linear or non-linear) dependencies between time series of suitable observables of the units, yielding edges (and/or their weights) of *functional networks.* These networks can severely differ from *structural networks*, also referred to as the *coupling topology* – consisting of actually existing connections between elementary units (e.g., physical or chemical). Knowledge about relevant (underlying) structural connections may be insufficient or even missing and hence, functional networks can be derived even though two units are (possibly) not structurally connected. Interactions themselves are manifested in many conceptually different ways, such as synchronization, flow of information or similarity.

While there is no one-fits-all analysis technique to assess or characterise interactions, there is a large repertoire of time-series- analysis techniques, based on different concepts emanated from statistics, non-linear dynamics, synchronization theory, information theory and statistical physics among others [6, 196–202]. These techniques utilize different signal characteristics (cf. Tab. I) with the aim to reveal certain properties of an interaction, while exhibiting various sensitivities [203].

We generally differentiate between three different properties of interaction.

The *strength of an interaction* is based on the assumption that more (abstractly) similar dynamics of observables deduced from pairs of units reflect a stronger coupling between these units. Deriving the strength of an interaction may focus on different dynamical aspects, such as amplitude distribution, relative phase positions, information content, etc. The quantification of the strength of an interaction therefore often yields the weight of an edge between two units in an undirected network.

Determining the *direction of an interaction* can allow to assess a *driver-receiver relationship* between two units. Estimators for the direction of an interaction are usually based on assumptions about cause and effect in the larger system, respectively on models for the temporal evolution of the dynamics of elementary units (e.g., utilizing Granger causality [204], transfer entropy [205, 206], partial directed coherence [207, 208] or phase modelling [209, 210]). In addition to the fact, that the driver-receiver relationship may be of bidirectional nature (both units are driver and receiver of the respective other), interpreting a numerical quantification of the direction of interaction poses a notorious difficult task. Generally, the sign of the numerical value of an estimator is an indicator for the direction of an interaction, with values close to zero either indicating the lack of interdependency or a bidirectional coupling between two elementary units, yet not informing about the actual strength of the interactions [211]. As there is of now no commonly accepted method to derive both strength and direction of an interaction, directed weighted networks are often derived combining estimators for the strength of interaction, to assign weights to the edges, and estimators for the respective direction. Nevertheless, due to the increased complexity of these networks, metrics to describe the characteristics of them are still limited.

The *functional form of interaction* describes the relationship between units – more specifically dynamical variables thereof – as a mathematical model, often expressed as coupling functions. While estimators for the functional form of an interaction can allow to derive a sufficient model for how units react/interact to/with each other, typically strong assumptions and/or in-depth knowledge about the involved dynamics and model parameters is needed [212–214].

| property of interaction | signal characteristic | analysis technique |
|---|---|---|
| strength | amplitude | (cross-)correlation |
| | phase | mean phase coherence |
| | information content | mutual information |
| | state space | non-linear interdependence |
| direction | amplitude | Granger causality |
| | phase | evolution map approach |
| | information content | transfer entropy |
| | state space | non-linear interdependence |
| functional form | phase | phase dynamics reconstruction |

TABLE I. Time-series-analysis techniques in use to characterise different properties of an interaction based on different signal characteristics. It is to be noted that in order to sufficiently employ these methods the system is required to be (at least approximately) stationary. Adapted from Chapter VIII.

With many of these techniques a distinction between direct and indirect interactions [176, 215] is not possible, raising the problem of transitivity and leading to the possible occurrence of spurious or superfluous edges in the network. Superfluous network constituents may also arise due to over- or/and undersampling of the system (*common sources* [176, 216, 217]), which again may result from difficulties of placing sensors in a sufficient manner, and lacking knowledge about the true structural organization. The issue of identifying superfluous constituents will be further addressed in Chapter III. Due to the high specificity of the different techniques regarding the property of an interaction, aspects of the dynamics, as well as spatial and temporal sensitivity, the choice of a fitting analysis technique depends on the specific problem in/of the complex system, as well as the investigated dynamical phenomena. Therefore, with no commonly accepted time-series-analysis techniques to infer the direction of an interaction and/or its respective strength, further advancing and conceptualization of novel techniques to reveal the intricate properties of interactions is inevitable.

As the mechanisms involved in the generation of dynamical phenomena studied in thesis relate to complex phase synchronization phenomena, we will focus on weighted undirected networks derived via *mean phase coherence* [218], a phase-synchronization-based estimator defined as follows:

$$R_{ab} = \left| \frac{1}{T} \sum_{i=0}^{T-1} \exp i \left[ \phi_a(t) - \phi_b(t) \right] \right| \qquad (17)$$

describing the strength of interaction between two units (vertices in a network, $\{a, b\} \in \{1, \ldots, \mathrm{V}\}$) with respect to the dynamical observables of the units and $T$ denotes the number of data points. Hence, $\phi_a$ are the instantaneous phases of the time series (of the respective observable) from unit $a$ (we use the Hilbert transform [219]). By definition, $R_{ab}$ is confined to the interval $[0, 1]$, where $R_{ab} = 1$ indicates fully phase-synchronized units.

The mean phase coherence has been shown to be robust under many influencing factors, such as noise [217, 218]. This estimator for the strength of an interaction [203] has been repeatedly employed, and with great success, to investigate many different systems, such as coupled oscillators [217, 220], climate systems [221–223], the cardiovascular system [224–226] and the brain [218, 227]. It hence poses a suitable estimator for the strength of interactions in the systems (with time-evolving coupling structures) investigated in this thesis (see Sec. I D).

### 4. Time-evolving networks

Many real-world systems can be considered to be (emergent) non-stationary complex dynamical systems. Such systems' spatiotemporal dynamics is influenced by their elementary units' dynamics and the interactions between the elementary units, which can manifest themselves in many different ways. Control parameters of such a systems' dynamic may change over time (e.g, coupling strengths or functions), as well as their underlying structural networks (e.g., coupling structure). Hence, deriving a single holistic static network to describe such systems is neither sufficient nor expedient and would potentially lead to severe misinterpretations. It is therefore more suitable to focus on the concept of time-evolving networks [72, 228], which have been successfully derived for dynamical systems (in many different scientific fields), such as epidemic spreading [229], citation networks [230, 231], the climate system [232] and the human epileptic brain (see Chap. VIII for an overview), just to name a few. As most analysis techniques to derive functional networks require the system to be (at least approximately) stationary to yield robust and reliable characterisations, commonly the time series of recordings of systems' dynamics are cut in succesive suitable segments. The duration of these segments has to be chosen in an appropriate manner, which poses a compromise between the approximate stationarity within a segment and statistical accuracy for characterisation [233, 234].

Generally, this is referred to as a moving-window approach (or sliding-window ansatz, cf. Fig. 6). It allows to derive a sequence of functional *snapshot networks* (associating each window/segment with a snapshot network), which represent non-overlapping temporal snapshots of the evolving functional network. While this approach allows a more suitable characterisation of the evolving functional network for the specific segments in time, detecting changes in the characteristics of the evolving functional network is rather difficult, as comparing snapshot networks is not an unambiguous task. Generally, comparing networks is notoriously difficult and poses an unsolved issue [77], as a intuitive approach to defining a distance metric between networks is highly nontrivial [235, 236]. Moreover, metrics for network comparison have been introduced with limited applicability for very specific systems [73–76, 78, 237–240] and with restrictions regarding the compared networks (e.g. equal in number of vertices or edges, equal edge density, equal degree-distribution, etc.). However, a direct comparison of networks as a whole can be circumvented by comparing network specific properties (e.g., utilizing the metrics introduced in Sec. I B 1) [79]. While certain network properties may not be compared in an absolute sense – due to limitations regarding their interpretation –, relative comparison for the respective snapshot networks can be suitable (e.g., the specific network property increases/decreases in time) and aid in gaining insights about the underlying systems. Utilizing different metrics to assess multiple local and global network characteristics, and how these characteristics evolve in time, will allow interpreting collective network changes in a contextual and integral manner, thus yielding a rather comprehensive depiction of the alterations of a time-evolving functional network. These again can be related back to properties of the respective system as well as to properties of the system's dynamics.

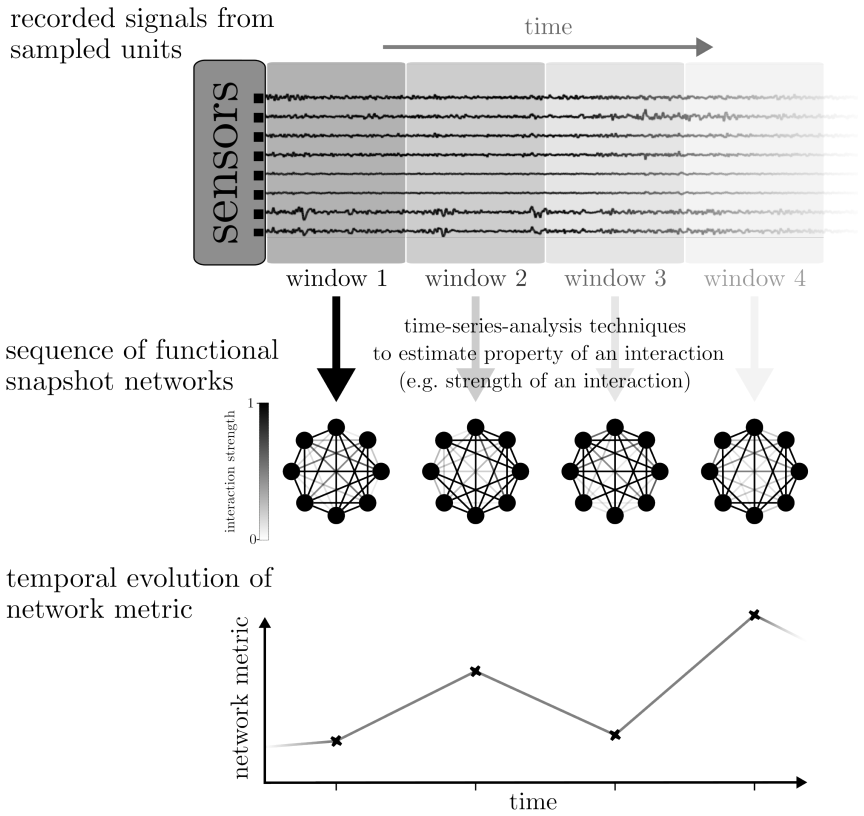


FIG. 6. Schematic depiction of the moving-window approach. Sensors record the signals/observables of sampled (elementary) units of the respective system. Time-series-analysis techniques are used to estimate properties of an interaction between these units, allowing to derive functional snapshot networks. For each snapshot network, metrics can be derived that resulting in a temporal sequence of metrics that allow to describe local to global network properties.

When interpreting changes in evolving networks, statistical validation of the interim results has to be considered [241]. If lacking appropriate models, the significance and the specificity of changes of the networks' properties can be verified via bootstrapping methods and Monte-Carlo simulations, such as *surrogate techniques* [192, 242–247]. By formulating an appropriate null hypothesis [248], the comparison to surrogates (on various levels in the chain of analysis), can verify the specificity of changes of networks' properties, and minimize the impact of confounding variables such as the influence of driving forces. On the level of the time series data, surrogate data is generated with the aim to preserve statistical aspects (e.g., mean, variance and distributional shape) and dynamical aspects (e.g., temporal or spatial patterns) of the original data, with exception of the property which is tested for [192, 249–252]. Likewise, on the level of networks, the preserved (global) property of a network surrogate might be e.g., the distribution of degree, strength or edge weights [194, 195, 231, 253, 254]. Both types of surrogates can respectively provide a rigorous framework for hypothesis testing and validation of methods. Surrogate data can be constructed by simulating realizations of an appropriate null model with Monte Carlo methods, which may include random sampling (from suitable probability distributions), model fitting (e.g., regression models), as well as estimating uncertainties and parameter optimization.

In order to accept or reject the defined null hypothesis, an appropriate statistical test (e.g., correlation or regression coefficients, means or variances, Kolmogorov-Smirnov test or Mann-Whitney $U$ test) is calculated for both original and surrogate data. The null hypothesis may be confidently rejected, based on the number of statistically independent constrained realizations, and if the respective discriminating statistics calculated from the original data fall outside the range of values calculated for the surrogate ensemble.

When it comes to interpreting changes, especially of local network characteristics (e.g., the centrality values of network constituents), multiple – usually in the order of number of vertices or edges – comparisons and statistical test are often conducted. This increases the likelihood of the null hypothesis being incorrectly rejected across all the comparisons (*family-wise error rate* FWER), which can be accounted for by correcting the significance levels (or $p$-values) using e.g., the Bonferroni method [255].

### C. Critical transitions and extreme events

Various natural, technological, and social systems have the capability to spontaneously generate vital and potentially harmful large-impact events [22, 256–261]. These so-called *extreme events* encompass a wide range of phenomena observed in nature, including solar flares [262, 263], earthquakes, tsunamis, extreme weather phenomena like heat waves, droughts, floods, heavy precipitation, and tornadoes in climate systems [264–268], extreme climate phenomena like El Niño, La Niña [269–272], rogue waves in oceans or optical systems [273–275], harmful algal blooms in marine ecosystems [276], large-scale blackouts in power networks [277, 278], market crashes [279–282], mass panics [283] and wars [256], fatal heart failure [284, 285], as well as migraine attacks [286] and epileptic seizures [287] in humans. Such events, while often assumed to be preceded by a critical transition, can result in unexpected and catastrophic outcomes when intersecting with susceptible human or natural environments. Therefore, investigating critical transitions and their entailed extreme events are in many ways of great scientific significance [288]. While some endogenous and exogenous factors that affect generation and extent of extreme events are known for some of these systems, the precise mechanisms underlying their emergence remain poorly understood. Hence, studies primarily focus on prediction, revealing mechanisms of emergence and termination, as well as the control of extreme events. From a physics perspective, extreme events in complex dynamical systems are defined as rare, recurring large deviations from the systems average global dynamics. It is to be expected, that for the majority of extreme events, abrupt excursions and significant deviations from an otherwise stable temporal evolution of a relevant observable holds implications about the extreme event and mechanisms involved in its generation and associated with a critical transition (cf. Fig. 9 (d)). Employing the network ansatz, deriving time-evolving functional interaction networks from relevant observables, has allowed to successfully gain deeper insights regarding extreme events in many of the above-mentioned systems, e.g., possibly enabling the identification of precursors of extreme events [289]. Yet, results achieved so far indicate mixed success. We will extend on this approach (see Sec. I B 4), focusing on network vertices and primarily on network edges – which represent the strength of interaction between vertices (elementary units in the system) –, utilizing centrality metrics (see Sec. I B 1), and with the aim to assess their role and involvement in the facilitation of the build-up of precursors and ultimately the generation of an extreme event. In Chapter V, we will investigate extreme events observed in networked-dynamical systems of *FitzHugh-Nagumo oscillators* (see Sec. I D 3). In Chapters VI and VII, we will investigate epileptic seizures in the human epileptic brain (see Sec. I D 4).

## D. Investigated systems

The investigated systems throughout this thesis can be categorized into two groups: static networks and time-evolving networks. We tested and evaluated (newly introduced) metrics on static (non-time-evolving) paradigmatic network models as well as social networks (see Chapters II). We employed novel methods and approaches to study time-evolving networks derived from coupled oscillator systems and the human epileptic brain (see Chapters V-VII)).

### 1. Zachary's karate club network

One of the most well-studied social networks is *Zachary's karate club network* [290]. Wayne W. Zachary conducted a study spanning three years, from 1970 to 1972, on the social structure of a university karate club. He constructed a weighted network consisting of 34 members, with documented connections between pairs of individuals (members of the club or associated with the club) who interacted outside club-related activities, which represents the networks edges (cf. Fig. 7). Edge weights are associated with the number of interactions between two individuals. During his study, a conflict emerged between the administrator, referred to as "John A" (vertex 34) and the instructor, known as "Mr. Hi" (vertex 1), resulting in the club's division into two factions. Half of the members formed a new club under the leadership of the instructor Mr. Hi, while others either sought a new teacher or discontinued their involvement in karate. Notably, Zachary accurately assigned nearly all club members to the groups they joined post-split, based on the collected data, with only one exception.

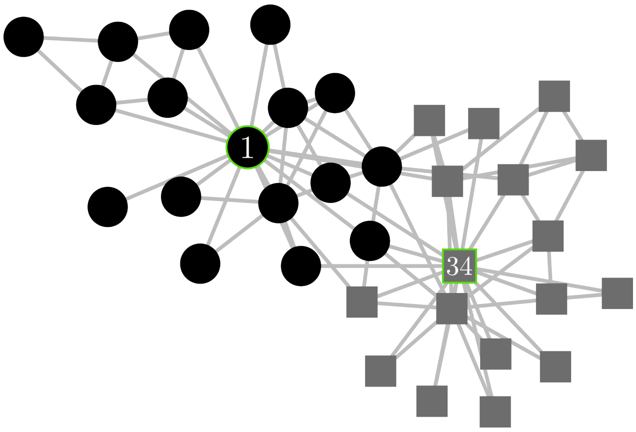


FIG. 7. Network representation of the social relationships in a university karate club consisting of 34 individuals. Individuals are represented by vertices (circles and squares) and interactions between these individuals are represented by edges (lines). The respective vertices of the two main characters, the administrator (vertex 34) and the instructor (vertex 1) are marked with green borders. The latter fission of the karate club into two groups is represented by vertices in the form of black circles (group that stayed with the instructor) and vertices in the form of grey squares (group that did not stay affiliated with the instructor). Adapted from Chapter II.

### 2. Commuter network of North Rhine-Westphalia

North Rhine-Westphalia (NRW) stands as Germany's most populous state, housing approximately 18 million residents across an expansive territory spanning over 34, 000 square kilometres. Remarkably dense in population, NRW rivals the German city-states in this aspect. The commuter traffic within NRW is exceptionally substantial [291] and by deriving a functional network based on this commuter traffic, structural aspects about traffic networks may be inferred. We associate the networks vertices with rural and urban districts in NRW, while the edges represent commuters travelling between them, with edge weights encoding the number of average daily commuters between two respective districts in the year 2017 (see Fig. 8, data collected by the *Statistisches Landesamt NRW - Statistik: 19321*). While this commuter network, derived from a real world system, not only poses a great testbed for novel network metrics, exploring the intricacies of it may hold significant promise for enhancing various aspects, including our comprehension and management of spreading processes.

FIG. 8. Average daily commuter traffic network of North Rhine-Westphalia (NRW) in the year 2017. Vertices (black dots and white border) represent districts in NRW (map in background). Vertex sizes represent the amount of inhabitants in the respective district. Edges (black lines) indicate commuter traffic between two districts. Edge widths represent average daily commuter traffic between the respective two districts. Adapted from Chapter II.

### 3. Coupled FitzHugh-Nagumo oscillators

The FitzHugh-Nagumo system (also referred to as FitzHugh-Nagumo oscillators), also known as the Bonhoeffer-van der Pol model, poses one of the most fundamental and extensively researched excitable systems [292–294], originally introduced as a two-dimensional simplification of the Hodgkin-Huxley model of spike generation in squid giant axons [295]. It provides a simplified yet effective representation of neuron firing dynamics using straightforward evolution equations [296]. Further, this non-linear model serves as a cornerstone in studying excitable behaviour in various fields, including neural and cardiac non-linear activities [297–299], social sciences [300] and material sciences [301, 302]. It has been instrumental in elucidating a wide array of phenomena, ranging from pattern formation [303–305] and firing cessation [306, 307] to noise-induced effects [308–314], diversity-driven oscillations [315, 316], and aspects of synchronization [306, 317–320].

In this thesis, we consider a network of $V$ diffusively coupled FitzHugh-Nagumo oscillators ($i \in \{1, \ldots, V\}$). The oscillators interact with each other through coupling terms, which represent the influence of one oscillator's dynamics on the others. This coupling generally can be excitatory or inhibitory, depending on the nature of the interaction between the oscillators. The $i$th oscillator of this network of $V$ coupled oscillators is described by the following equations of motion:

$$\begin{aligned}\dot{x}_i &= x_i(a_i - x_i)(x_i - 1) - y_i \\ &\quad + \frac{\kappa}{V-1}\sum_{j=1}^{V} A_{ij}(x_j - x_i) \\ \dot{y}_i &= b_i x_i - c_i y_i\end{aligned} \tag{18}$$

Here, $x_i$ is known as the excitatory variable and $y_i$ is known as the inhibitory variable of the $i$th oscillator. Further, $a_i$ , $b_i$, and $c_i$ are internal parameters of the $i$th oscillator, $\kappa$ is the global coupling strength, and $\mathbf{A} \in \{0, 1\}^{V \times V}$ denotes the adjacency matrix of the coupling structure.

The dynamical behaviour that can be exhibited by a network of coupled FitzHugh-Nagumo oscillators depends on various factors, including the strength and type of the coupling between oscillators, the coupling topology, the control parameters of the individual oscillators, and potential external inputs to the network (cf. Figs 9). The dynamics exhibited by such a network of coupled FitzHugh-Nagumo oscillators, covers a wide range from rhythmic behaviour characterised by periodic oscillations, synchronization and desynchronization, over the emergence of complex spatio-temporal patterns, to extreme events [319, 320, 322, 323]. Here, extreme events express themselves as rare, yet recurring high-amplitude oscillations observed in (almost) all oscillators [322]. Due to these deterministic model systems of coupled FitzHugh-Nagumo oscillators being capable of generating extreme events, they pose a great framework to study the underling generating mechanisms of extreme events, a topic which we will pursue in Chapter V. There we will investigate which edges in networks of coupled, excitable FitzHugh–Nagumo units facilitate the recruitment of non-excited units into the final generation of an extreme event, utilizing novel edge-centrality concepts and network decomposition techniques to assess the edges' role in the network.

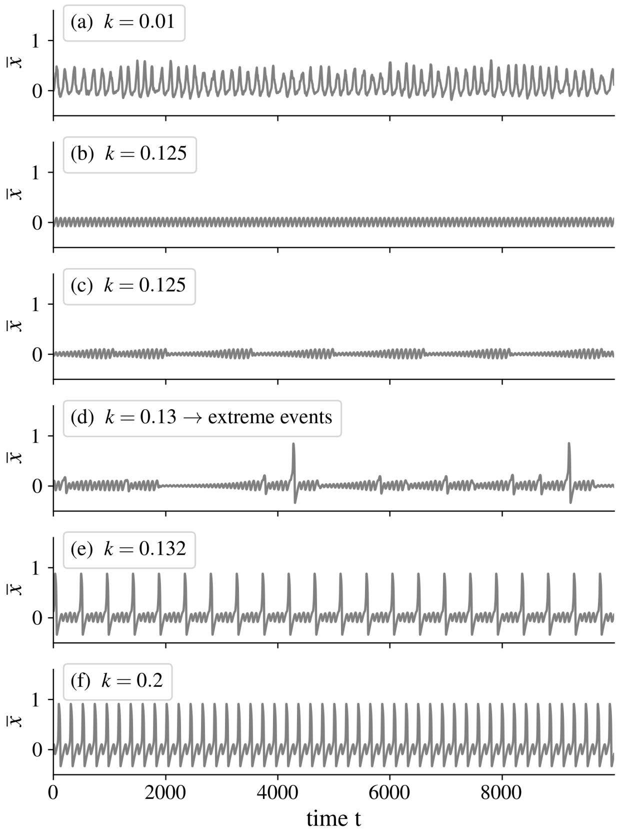


FIG. 9. Range of dynamics exhibited by an exemplary small-world network of coupled FitzHugh-Nagumo oscillators displayed in the mean of the excitatory variable $\overline{x} = \frac{1}{V}\sum_{i=1}^{V} x_i$. Parameters were set to $V = 20$ vertices, $E = 200$ edges, rewiring probability $p_r = 0.25$, internal parameters $a_i = a = 0.02651 \forall i$, $c_i = c = 0.02 \forall i$, $b_i = 0.006 + \frac{i-1}{V-1} 0.008$ $(0.006 \leq b_i \leq 0.014 \forall i)$, coupling strength $k$, and randomly chosen initial conditions for $x$ and $y$ in each realization (a) to (f). Each time series was generated via the integration of Eq. 18 with the adaptive, explicit Runge–Kutta method of fifth order [321] and a step size of 1 and at least $10^4$ initial transients were discarded.

### 4. The human epileptic brain

The human brain is not only one of the most interesting and complex organs in the human body, but probably also the most complex dynamical system in nature known to men. It contains about 86 billion neurons (and about trice the amount of glial cells) communicating with each other through synapses [324], electromagnetic fields [325] and chemical processes [326, 327]. Each neuron can have thousands (up to 200000) of synaptic connections with other neurons. This amounts to approximately a trillion synapses, which strung together would cover a distance of hundred of thousands up to a million kilometres, being longer than the distance between earth and moon.

Therefore the structural makeup of the human brain contains different highly connected local networks spanning different spatial scales, starting from single cells and synapses, over cortical columns, to (sub)cortical areas. These networks neither follow complete random topologies nor are they deemed highly regular. It is to be considered, that all these different networks on different spatial scales, are again connected, forming a *network of networks*, capable of exhibiting an immense variety of different cognitive and behavioural functions. The functional capabilities of this complex dynamical system is largely similar in most human beings [328–334] despite certain differences in morphologies and structural make-up. Generally, in case of many diseases of the brain, normal, (healthy) as well as pathological functions and structures coexist [335]. The human epileptic brain differs from the "non-epileptic human brain" especially in its exhibition of epileptic seizures [336]. Epileptic seizures as extreme events [287] are defined as a transient occurrence of symptoms due to abnormal excessive or synchronous neuronal activity in the brain. Seizures can be caused and triggered by a variety of different factors, including genetic predisposition or physiological trauma. Having experienced at least one seizure, with a probability of at least 60% for further seizures in the next 10 years [336] qualifies for the clinically diagnosis of epilepsy. This diagnosis holds a great burden for affected people, not least to comorbidities [337], psychosocial and economical impairments [338, 339], social stigma [340] and seizures [337, 341], ultimately due to the large impact, potential complications, and foremost the unpredictability of seizures [342–345]. Epilepsy is the third most common neurological disorder, with 50 million people diagnosed worldwide [346]. About two-thirds of these people are sufficiently treated, while for the remaining, intensive diagnostic, polytherapies and non-pharmaceutical interventions (e.g., surgery, neurostimulation) pose alternatives, often associated with even greater risks and possible side effects. Comprehending the emergence, spread, and cessation of epileptic seizures is widely regarded as pivotal for grasping the essence of epilepsy. This understanding is key for developing diagnostic methods and treatment strategies.

The brain is a complex network of non-stationary and interacting subsystems, whose spatial-temporal dynamics is largely influenced by properties of exactly these interactions. Hence, epilepsy is now-a-days considered a network disease. This paradigm shift from focusing solely on discrete cortical areas as the origin of seizures to recognizing the existence of widespread epileptic networks spanning across lobes and hemispheres has significantly deepened comprehension of epilepsy. Treating epilepsy as a network diseases will further shape both research endeavours and clinical approaches to treating this complex and impactful neurological disorder. Recent advances in understanding brain dynamics (varying on multiple scales), utilizing the network ansatz and the concept of evolving (functional) brain networks, are extensively reviewed, apart from this thesis, in Bröhl and Lehnertz [139].

It is important to highlight that many complex networks in nature (such as epileptic brain network), however, are not static but evolve in time, which shows the necessity for (novel) approaches to not only infer time-evolving interaction networks from empirical data but also characterise said networks to gain a deeper understanding of the complex dynamical system human epileptic brain and its dynamics (see Sec. I B 3 - I B 4). Various imaging and recording methods are available for evaluating the structure and dynamics of a time-varying epileptic brain network across various spatial and temporal scales, with differing levels of invasiveness.

In this thesis we mainly focus on *electroencephalography* (EEG) to record human brain dynamics, as it is the only technique capable of long-term continuous recordings up to months [347–349]. Electroencephalography (EEG) is a technique used to record electrical

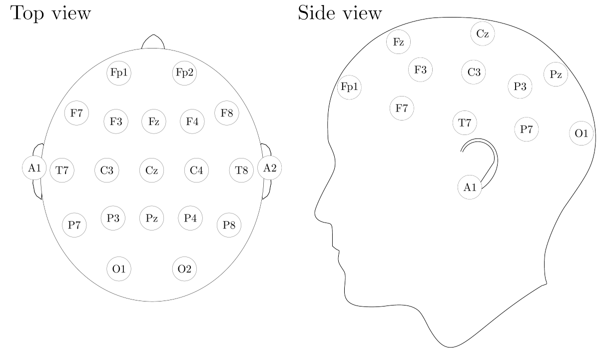


FIG. 10. Schematic of sensors/electrodes (depicted as white circles with black border) placed on a human head in the standardised 10-20 system. (Left: top view, right: side view)

activity of the brain [350–352]. This electrical activity is assumed to result from the firing of neurons, which generates electrical fields that can be measured even outside of the skull as voltage differences at various electrodes. It is to be noted the positioning of electrodes can result in issues of over- and undersampling. Especially an overly dense spatial sampling can ultimately lead to the introduction of superfluous information (on several levels of the investigation) due to the presence of common sources [217], a problem that has to considered, and potentially accounted for, when it comes to interpreting certain observations.

Electrodes are usually placed on the scalp at specific locations according to international standards (such as the 10-20 system [353, 354] depicted in Fig. 10) to ensure consistent and reproducible placement across individuals. However, EEG measures electrical potentials of the brain without a clearly defined ground, primarily for safety reasons [355–362]. Consequently, EEG signals are differential measurements, meaning they represent the voltage difference between two recording sites. Therefore, the choice of a reference electrode is to be made, which can significantly affect the interpretation of EEG data. In Chapters II and IV of this thesis, we will investigate EEG data recorded from electrode sensors placed according to the 10-20 system, with the inter-hemispheric sensor CZ as the chosen reference to avoid unilateral imbalance from the hemispheres. In Fig. 11, we display exemplary EEG recordings of such sensors, differentiating between dynamics presumably unrelated to an epileptic seizure, the dynamics associated with the critical transition prior to an epileptic seizure, and the focal onset of an epileptic seizure.

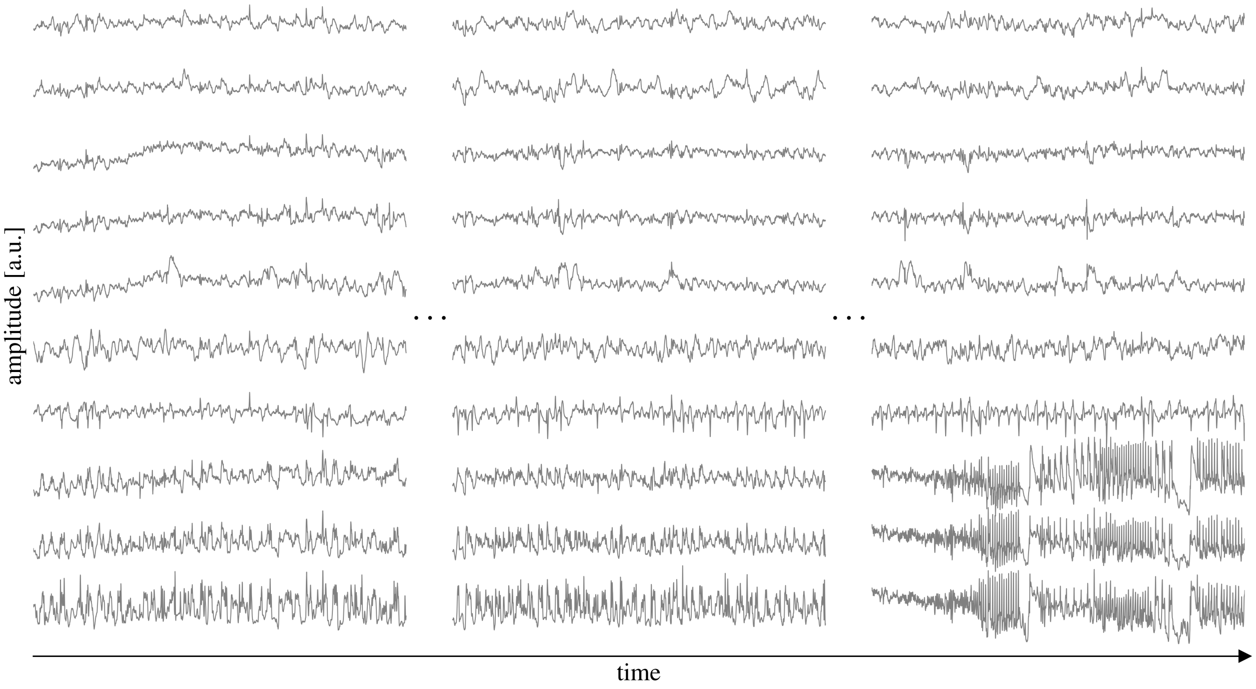


FIG. 11. Exemplary electroencephalographic recordings of multiple electrodes from a subject with epilepsy. Excerpts of 30 s duration from different brain regions (top to bottom) during times far off seizure-related dynamics (left), during a critical transition (middle), and at onset of a focal seizure (right). Adapted from Chapter VII.

Further in Chapters VI and VII we will investigate data recorded via *intracranial EEG* (iEEG), a technique to measure electrical activity directly from the surface of the brain or from within deep brain structures [363]. To this purpose, dedicated electrode sensors are directly placed onto and into the brain tissue, posing a deliberately invasive technique. In many cases, iEEG provides a more detailed and precise source of information, as problems common for EEG, such as muscle and skin conductance artefacts, are circumvented, which increases the signal-to-noise ratio drastically (factor of $\approx 100$) [364]. Yet, and despite numerous other advantages, iEEG poses certain risk, mainly related to the surgical implantation of foreign objects into a system as sensitive and adaptive as the human brain. Hence, iEEG is primarily used for pre-surgical evaluation for epilepsy surgery [365] and mapping functional brain areas [366, 367]. The quantity and specific anatomical placement of intracranial sensors and choice of reference are tailored exclusively to suit the unique requirements of each individual, resulting in considerable variability rather than uniformity.

## E. Structure of this thesis

In the following **Chapter II** we introduce a novel edge-centrality metric derived from generalizing the degree and respectively strength concept for binary and weighted networks. We highlight the complementary nature of this edge centrality metric with regard to more prominent ones by employing the novel metric to investigate paradigmatic network models as well as real-world networks from various scientific domains. Furthermore, we show the novel centrality concept's suitability to identify central edges in these networks.

**Chapter III** tackles the issue of how to identify and avoid potentially superfluous network constituents, e.g., resulting from spatial or temporal oversampling of the system's dynamics when constructing networks from empirical time-series data. Hence, we introduce a perturbation-based method to identify potentially superfluous network constituents utilizing vertex and edge centrality concepts and illustrate its suitability by investigating paradigmatic network models.

In the following **Chapter IV**, we engage on EEG-derived evolving functional brain networks, and explore the potential influences of biological rhythms on the importance hierarchy of constituents – as derived with different complementary vertex and edge centrality concepts – in these networks. Specifically, we reveal the influence of circadian and ultradian rhythms on this time-varying importance of constituents integration in the network, which holds intricate indications about the existence of distinct subnetworks, generally involved in ongoing brain activities during sleep and wakefulness.

In **Chapter V**, we firstly bring extreme events to focus, investigating networked dynamical systems of coupled FitzHugh-Nagumo oscillator networks. As these oscillators networks are able to exhibit rare and recurrent events, fitting our definition of extreme events, they pose a suitable testbed to investigate the generation of extreme events in greater detail. Again, we derive functional time-evolving networks from the time series of the oscillators' dynamics, employing the edge-centrality concepts and edge-based decomposition techniques to study the role of certain edges and groups of such for the generation of extreme events. We are able to reveal that the majority of edges which facilitate the build-up of precursor structures of extreme events, do not have an equivalent in the underlying coupling topology of the oscillators.

We continue our study of extreme events in **Chapter VI** focusing on epileptic seizures in the human brain, further engaging on iEEG-derived evolving functional brain networks from a large but inhomogeneous group of subjects with pharmacoresistant epilepsies with different anatomical origins. We investigate the temporal changes of vertex centrality values from multiple complementary vertex centrality concepts and are able to identify specific vertices that carry information predictive of impending seizures. From there on, we are able to formulate several possible network reconfiguration scenarios that describe alterations of the evolving epileptic brain network specific for pre-seizure periods. Surprisingly, these reconfigurations virtually include all network constituents, representing the various brain regions as well as the functional connections between them in contrast to the common believe of a focal generation.

Hence, in **Chapter VII** we revisit the data and further investigate excitable complex networks of FitzHugh-Nagumo oscillators, delving into research on network constituents that carry predictive information about impending seizures, focusing especially on networks' edges by utilizing edge centrality concepts. For the time-evolving functional brain networks we take into account the influence of diverse biological rhythms on the temporal evolution of the importance hierarchy and therefore additionally investigate the local temporal change of centrality values. Overall focusing on networks' edges not only allows us to paint a more comprehensive picture about constituents involved in the generation of extreme events, as well as how predictive vertices and edges are related to each other, but further reveal that the majority of these constituents form a large complex tipping subnetwork, generally involved in mechanisms that drive these complex dynamical systems into processes involved in the generation of extreme events.

Finally, in **Chapter VIII** we present a review, which discusses and summarizes the conceptual basics of network theory with specific regard to describing and characterising time-evolving human epileptic brain networks. We highlight current shortcomings as well as the potential developments towards improved clinical management of epilepsy utilizing the network approach.

To conclude, in **Chapter IX** a short summary of the conducted research, as well as an outlook and closing remarks are given.

# II A straightforward edge centrality concept derived from generalizing degree and strength

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Many natural and man-made networked systems, such as brain networks [56], climate networks [43, 368], food-webs [369] or social networks [370, 371], have been successfully investigated by employing complex network approaches. In diverse areas of science [7, 36, 39, 42, 49, 62, 125, 372], this ansatz allowed to gain deeper insights into structure and dynamics of spatially extended complex systems, describing the system by an interaction network with vertices representing elementary units and edges representing interactions between them. In investigating such interaction networks it is of vital interest to identify key network constituents and characterise their importance for a network's structure and/or dynamics [64, 139, 153, 373–377]. A growing number of different concepts and metrics, which can be abstracted as centralities, aim to characterise the role of network vertices for structure and dynamics [378]. Yet, in contrast, rather few akin concepts and metrics have been defined to characterise the role of network edges for structure and dynamics.

In prior research, Timo Bröhl extended and modified closeness and eigenvector centrality concepts for vertices to those for edges, and further demonstrated their usefulness in gaining additional information about network constituents for various paradigmatic and real-world topologies [155]. Most other of those edge centralities also focus on path-structural aspects [124, 379–384], the concept of bridging [385–388] or are based on the spectrum of the network's Laplacian [389, 390]. Surprisingly, there has been no definition of an edge centrality concept, analogously adapted from the historically first and conceptually simplest vertex centrality [114], namely vertex degree centrality. Therefore, Timo Bröhl proposed such an analogously defined edge centrality concept, termed nearest-neighbour edge centrality. With this novel edge centrality concept the authors aim to assess the integration of an edge within its local neighbourhood in the network, much like vertex degree/strength centrality assesses the integration of a vertex to its neighbouring vertices. In order to illustrate this edge centrality concepts' added value and novelty, Timo Bröhl compared this novel concept to aforementioned edge centrality concepts, edge betweenness, edge closeness and edge eigenvector centrality. With this rather holistic approach to combine the results of multiple complementary centrality concepts the authors aimed to investigate the integration of network edges. Interpreting this integration, based on a single or multiple centrality concepts can then ultimately aid to understand specific structural and dynamical phenomena in the network. For this purpose, and to show this novel concepts general applicability, Timo Bröhl employed the nearest-neighbour edge centrality to identify important edges in a commonly used benchmark model in social network analysis, namely Zachary's karate club, a commuter network of Germany's most populated state North Rhine-Westphalia (NRW), an evolving epileptic brain network derived from iEEG recordings, as well as in paradigmatic network models. Indeed, investigating correlations (Pearson correlation coefficient) of edge ranks obtained with the different centrality metrics from investigating paradigmatic network models of different sizes, revealed that the nearest-neighbour edge centrality provides non-redundant information about the networks' edges, although observing correlations to the conceptually related concept of edge eigenvector centrality. In the investigations of Zachary's karate club network, employing the nearest-neighbour edge centrality, Timo Bröhl was able to identify, both, global as well as local bottleneck structures in the network. These bottleneck structures can bee associated with a global fission of the network into two groups centred around two key figures (vertices) of the network. In contrast to this, edge betweenness centrality allowed to highlight a global bottleneck structure, while edge closeness and edge eigenvector centrality highlighted rather unspecific edges connected to the two most influential vertices of the network. Hence, Timo Bröhl was able to deduce, that despite the definition of the nearest-neighbor edge centrality being based on local network properties, it still allows to characterise aspects of the path structure in a complex network.

Further, Timo Bröhl investigated a commuter traffic network, where the rural and urban districts in North Rhine-Westphalia constitute the networks vertices and edges representing the commuter traffic between two districts, with the edge weights equalling the average number of commuters travelling between the two districts on a day in 2017. In contrast to edge betweenness, edge closeness and edge eigenvector centrality, nearest-neighbor edge centrality identified edges to be important that are far off the expected commuter centres of NRW, being the population-dense districts. Rather, edges between urban districts, with neither a large population density nor a high commuter volume, were highlighted, as the total commuter traffic in and out of them is comparably high. The latter may allow to consider two districts, generally deemed urban, as one larger district. Timo Bröhl hypothesized, that these insights gained with the nearest-neighbor centrality may hold intricate but vital information about possible spreading phenomena on such networks (e.g. pandemic spreading) and how countermeasure can be formulated and employed.

Additionally, Timo Bröhl investigated an evolving functional human brain network during an epileptic seizure, derived form iEEG recordings (see Chap. I B 4 and Chap. I D 4). The recording was separated into four blocks (pre-seizure, first half of the seizure, second half of the seizure, and post-seizure) of equal duration. Each block contained equal amount of consecutive snapshot networks. Employing the nearest-neighbor edge centrality concept for each snapshot network and reporting on the aggregated centrality values for each block, allowed to identify that the most important edges, prior and after the seizure, are predominantly located in the hemisphere associated where the seizure was (clinically) assumed to originate from. These edges were further connected to vertices associated with the clinically defined seizure onset zone. During the seizure these central edges were rather connecting nearby vertices in homologous regions in the opposite brain hemisphere. Timo Bröhl deduced that characterising important edges in evolving functional brain networks can possibly aid in improving and advancing the understanding of the complicated spatial-temporal dynamics of epileptic seizures.

Combining the individual results from investigations of paradigmatic and real-world networks, highlighted that the nearest-neighbor edge centrality concept, despite the expected conceptual similarities to other edge centrality concepts, provides additional and non-redundant information about of edges in a network. Particularly in situations were path-based and/or more global centrality concepts have limited significance, such as local spreading phenomena, employing nearest-neighbor centrality can potentially be considered to be much more advantageous. The authors further deduced that extensions – to binary and/or directed networks, networks of networks [391], multigraphs [91], or hypergraphs [392, 393] – can be achieved in a rather simple by manner taking into account in- and out-degree/strength of vertices and that nearest-neighbor edge centrality concept will help to improve the characterisation of networks through a data-driven identification of important edges.

# III A perturbation-based approach to identifying potentially superfluous network constituents

Timo Bröhl and Klaus Lehnertz
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Analysing real-world complex systems often harbours the problem that explicit knowledge of structural organization of the dynamical system under study is limited or simply not accessible [7, 36, 39, 40, 42, 43, 49, 56, 60, 62, 125, 372]. In these cases, the complex network approach is still a useful and successful ansatz to gain deeper insights into structure and dynamics of spatially extended complex systems, describing a system as an interaction network with vertices representing elementary units and edges representing interactions between them. Henceforth, in real-world applications the interaction networks' vertices are quite commonly associated with sensors that are placed in sufficient manner to capture the dynamics of said elementary units. Many different time-series-analysis techniques are utilized to derive edges via a data-driven quantification of interaction properties from the system's dynamics. Nevertheless, severe misinterpretations of network properties may result from the fact that the reliability of these techniques is limited by the unavoidable finiteness of noisy field data and the fact that there is no commonly accepted method to derive binary or weighted networks from interactions properties [176, 177, 191, 217, 394–397]. These issues, however, are further influenced and preceded by the more general problem of choosing the right number of sensors and their respective meaningful placement. As this poses a highly non-trivial task, a spatial over- or undersampling of a system is largely an inevitable outcome. In the network approach, over- or undersampling directly translates to the presence of potentially superfluous or the absence of potentially relevant network constituents, ultimately leading to severe misinterpretations of network properties [176, 177, 191, 193, 217, 394–399]. As the usual approach in investigating real-world systems is to gather as much information as possible, oversampling appears to be the more prominent issue. A vast plethora of methods [156, 398, 400–402] have attempted to identify redundant edges, and while the suitability of these approaches is still a matter of debate [403–406], the identification of superfluous vertices has been tackled to a much lesser extend [407, 408]. Timo Bröhl developed a perturbation-based approach to identify potentially superfluous network constituents. An elemental and minuscule perturbation directly targets a single network constituent with the assumption, that if the targeted constituents is indeed superfluous, network characteristics will largely be left unaltered after the employed perturbation. The authors focused on three elementary perturbations: vertex removal, vertex cloning and edge removal. Timo Bröhl tested the suitability of the novel approach on weighted paradigmatic network models, investigating perturbation-induced changes in multiple global and local network characteristics, approximating that these characteristics in their sum capture a somewhat sufficiently holistic description of the network. For a given realization of a network, the authors estimated these network metrics prior to any perturbation. In a next step, and for each network constituent respectively, they employed the respective perturbation and re-estimated the respective network metrics, quantifying the influence of the network perturbation via the average percentage change of the respective metric. Timo Bröhl confirmed the general expectation, that independent of the investigated real-world system, certain network topologies can contain superfluous constituents, due to the structural makeup of the network. Indeed, the investigated effects of employed perturbations did largely differ for different network topologies, sizes and edge densities. Regular network structures where especially prone to be influenced in their local characteristics, while global network characteristics were mostly left unaltered. Yet and here irrespective of the networks topology, Timo Bröhl further revealed strong dependencies regarding the importance of the constituent targeted by the perturbation. The authors assessed constituents' importance and the networks' importance hierarchies via different and complementary centrality concepts for vertices and edges. Contrary to expectation, using the perturbation-based approach, the authors were able to reveal that there are far less potentially superfluous constituents in complete and regular networks than in more complex topologies such as small-world and scale-free networks.

The authors showed that especially for real-world complex systems, for which a priori knowledge about the network's actual structure is either limited or simply not accessible, the perturbation-based approach can aid in identifying potentially superfluous and likewise indispensable network constituents. Furthermore, the authors investigations pave the way for future studies that focus on employing the presented approach to identify potentially superfluous constituents in networks with built-in superfluous constituents, i.e.. via some form of cloning network constituents [193], and even in networks constructed from empirical observations of real-world systems prone to have superfluous constituents, ultimately aiding in a more accurate modelling of real complex dynamical systems.

# IV Impact of biological rhythms on the importance hierarchy of constituents in time-dependent functional brain networks

Timo Bröhl, Randi von Wrede and Klaus Lehnertz

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Various natural and endogenous cycles with different period lengths influence the human body on multiple levels, from blood circulation, pulse, hormonal cycles, over bowel activity to different sleep stages. It has been well known for more than 50 years, that biological rhythms, infradian ($>$ 24 h), circadian, (24 h) as well as ultradian rhythms ($<$ 24 h), impact electroencephalographic (EEG) signals [409] of the human brain. As many endeavours to describe the complex dynamical system brain are based on EEG recordings, either assessing the dynamics of few brain regions or/and covering timescales from a few seconds to some hours, it is close at hand, that the influence of biological rhythms will impact tailing investigations. While the network approach [36, 71, 410] has successfully and repeatedly shown to provide novel and important insights into complex dynamical systems such as the brain [56, 62], many earlier studies described a static network. Yet, modelling many systems via time-dependent/evolving networks [72, 411] allows a potentially more detailed and accurate description. This holds true especially for biological networks, such as the brain, for which dependencies on different time-scales have been observed. Many different network metrics yield a broad applicability to describe global to local aspects in network terms, which can be related to properties of the described systems. A highly relevant aspect in investigating such systems is to identify key network constituents, which can aid to understand and control these networks with respect to the network structure and dynamics. characterisation of a network constituent's role is achieved through different methods and metrics, which can be generalized under the concept of centrality. While many of these concepts focus on evaluating a vertex' role [35, 412–414] in the network's structure and dynamics, recently introduced modifications to vertex centrality concepts [127], novel [154] , as well as some few established edge-centrality concepts [124, 147] focus on achieving an analogue for edges.

Importance hierarchies yielded from employing (multiple different) centrality concepts to evolving functional brain networks – which are estimated from EEG-data –, are expected to be influenced by circadian rhythms. Extending on recent studies [415–419], the authors investigate the influence of circadian rhythms on the importance hierarchies of the constituents of evolving functional brain networks, associating sampled brain regions with networks vertices and time-evolving interactions between these brain regions with networks edges. Timo Bröhl analysed EEG signals, continuously recorded over multiple days, from five subjects with disorders and three subjects without disorders of the central nervous system. He estimated the time-dependent, fully connected, weighted functional brain networks from the respective EEG recordings (see Chap. I B 4 and Chap. I D 4), and tracked the changes in the importance hierarchies of network constituents [420, 421], which are possibly related to biological rhythms [422]. The importance hierarchies of each snapshot network were estimated via four complementary vertex and edge centrality concepts, respectively.

The authors observed notable contributions of circadian rhythms and ultradian rhythms on certain network local characteristics, independent of the employed centrality concept and for all subjects. Nevertheless and contrary to expectation, Timo Bröhl observed the temporal sequences of centrality values of some brain regions to be much larger impacted by circadian and ultradian than other brain regions. Furthermore, the strength of this impact differed when considering different centrality concepts, which highlighted (different) specific structural aspects of a network, such as the path-structure or the strength distribution. Timo Bröhl showed that when combing the results yielded by different centrality concepts, almost all network constituents were impacted by the circadian rhythm in all subjects. While the authors were not able to deduce a trivial relation between the influence of the circadian rhythm and a constituent's importance, they were able to observe vital and fundamental subnetworks within the evolving functional brain networks. These subnetworks were constituted by vertices and edges that showed pronounced influences by the circadian rhythm in their respective temporal sequence of centrality values. On the one hand, the authors were able to identify a subnetwork comprising specific brain regions from both hemispheres, while on the other hand, the authors identified this subnetwork to have nuanced but distinct differences during night-time than during day-time. These observations let the authors to hypothesize about possible relations to the concept of a resting-state network [423]. Due to the night-time-specific alterations of the evolving functional brain networks, Timo Bröhl further investigated possible day/night patterns in the temporal evolution of the centrality values of vertices and edges. The authors were able to reveal major differences regarding the largest changes in centrality values between night- and daytimes, which revert back to the vital subnetworks. During night-time, specific brain regions were highlighted, an observation which the authors contributed to memory consolidation processes during sleep [424, 425]. During day-time, brain regions were highlighted that consolidate spatial and visual information and integrate perceptions with other sensory inputs. Overall the authors observed strong influences of the circadian and ultradian rhythms on the importance hierarchy of network constituents in time-dependent functional brain networks, highlighting distinct and possibly fundamental subnetworks, that are generally involved in ongoing brain activities.

# V Identifying edges that facilitate the generation of extreme events in networked dynamical systems

Timo Bröhl and Klaus Lehnertz

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Extreme events exhibited by dynamical systems in nature, ranging from natural over technological to social systems, are ubiquitous and pose real and often times unpredictable constraints on humans and the world that we live in [22, 256–261]. Whether blackouts in power grids [426–429], extreme weather events in our climate system [264–268, 430–438], the extinction or overpopulation of species in the ecosystem, market crashes in economical systems [280, 282, 439], cardiovascular diseases like heart attacks [284, 285] or epileptic seizures in the human brain [377, 421], understanding the dynamical underpinnings of generation of such extreme events is vital for understanding, predicting, and controlling them. While some aspects of dynamical mechanisms involved in the generation of extreme events have been recently studied with great effort, the knowledge about the involvement of potential pathways in networked dynamical systems is limited. Identifying such pathways can lead to further advances in the study of extreme events, as they may play vital roles in facilitating the build-up of precursor structures and ultimately the generation of extreme events. Therefore a growing interest in if and how the coupling structure of spatially-extended complex systems is involved in the generation and exhibition of extreme events has led to many advances in research from different perspectives of science [119, 266, 267, 322, 440–446] and was a further motivation for the authors to conceive this research project.

Yet, most of the prior research employed either concepts assessing global network characteristics or specifically characteristics of vertices in the networks. However, as in interaction networks edges represent attributes of an interaction, e.g. strength, direction, or the coupling function, between two vertices, (time-evolving) properties of edges and their integration in the network can hold vital information about the generation of extreme events in the network. Therefore in this publication the authors conceived a research project focusing on an improved characterisation of the role of edges (in relation to the role of vertices) in networks, to study the generation of extreme events in networks in greater depth.

In order to shed light on the role of specific edges in the network, Timo Bröhl employed various complementary centrality concepts. These concepts were partly introduced in prior research (cf. Chap. I B 1). He further proposed a network decomposition technique based on edge centrality, that allows to identify sets of edges in a hierarchical structure of importance. In this context, Timo Bröhl studied complex networks of excitable units of FitzHugh-Nagumo oscillators, deriving time-evolving interaction networks by investigating the strength of interaction from time series of the units' dynamics estimated with bivariate analysis techniques and using a sliding-window approach. The FitzHugh-Nagumo oscillator (or model) is not only a paradigmatic model of an excitable system and hence a commonly used model for neural dynamics [447] and excitable behaviour in cardiac non-linear activities [298], but further, if multiple FitzHugh-Nagumo oscillators are coupled, they can mimic diffusion-like transport processes between them. Hence, such networked dynamical systems of coupled FitzHugh-Nagumo oscillators are known to be able to exhibit self-generating and self-terminating, high-amplitude, rare, yet reoccurring deviations from their regular dynamics, without influencing factors of noise or parameter changes [322, 374, 448–450], and hence fulfilling the criteria for an extreme events from a physics perspective. For a fixed number of oscillators, Timo Bröhl constructed multiple networks of coupled FitzHugh-Nagumo units with different coupling topologies (and a different number of edges) paradigmatic for many networked dynamical systems found in nature.

While previous studies have revealed that extreme events in such systems are preceded by so-called proto-events in certain units of the system [322, 450] – which has also observed in other excitable systems [451–460] – the recruitment of other units remained to be investigated. Successfully tackling this challenge, in this publication, the authors were able to conjecture that, independent of the respective underlying coupling topology, such a recruitment is facilitated by certain (sets of) edges in the network. These edges are either considered to be the least or the most important edges (with the different centrality concepts). This is partly in accordance to prior research, as it was revealed that units, which are less strongly interconnected in the network are the units that initiate extreme events [450]. These (sets of) edges appear to have no respective equivalent in the underlying coupling topology of the networked dynamical system of coupled FitzHugh-Nagumo oscillators. The authors conclude that these findings together with a more comprehensive description of the role of specific edges – considered to be involved in generation of extreme events – can aid to gain further insights into the mechanisms of the generation of extreme events in many natural networked dynamical systems. This might ultimately lead to advances regarding the control of a system (and its dynamics) via targeted minuscule perturbations [443, 444] (cf. Chapter III) of specific pathways or single functional edges.

# VI Reconfiguration of human evolving large-scale epileptic brain networks prior to seizures – an evaluation with node centralities

Rieke Fruengel, Timo Bröhl, Thorsten Rings and Klaus Lehnertz

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Epilepsy is not only one of the most common neurological disorders observed, accounting for 0.5% of the global burden of disease [346] and affecting over 50 million people worldwide, it is also a disorder of a, if not the most complex dynamical systems known to man, the human brain. Epilepsy is characterised by the recurrence of seizures, which are considered to be (the result of) spontaneous, abnormal and excessive electrical activity in the brain. Epileptic seizures, their apparent unpredictability, and stigmatization of epilepsy itself poses a huge burden for people with epilepsy but also their relatives and people close to them. Yet, still today the treatment of epilepsy is a complex and evolving endeavour, as the brain is a complex and adaptive dynamical system. For about one third of people with epilepsy, pharmacological treatment is rendered insufficient [461], causing the need for alternative treatment options such as neurostimulation or surgical intervention, with the latter allowing about 70% of those pharmacoresistant people with epilepsy to remain seizure-free for at least one year after surgery [462]. Nevertheless, long-lasting freedom from seizures is still a goal to be achieved for most of the affected people, even after surgical intervention and removing the clinically defined seizure onset zone (SOZ). The latter especially emphasizes the need to further investigate seizure generation and to reveal seizure generating mechanisms in humans. In general, it is of utmost importance to understand, predict, and possibly control epileptic seizures, which can bring about the development of novel treatment options [377]. Such advances may include warnings about impending seizures, employing targeted interventions and countermeasures prior to seizure generation or even stopping seizures, which ultimately has the potential to alleviate the burdens this disease entails.

Epileptic seizures can be considered extreme events in the most general definition of rare, yet recurring large deviations from a system's average dynamical behaviour. Hence, epilepsy in the human epileptic brain, from a perspective of physics, poses a vital opportunity to study the phenomena of extreme events in complex dynamical systems.

In the last decade, utilizing the network ansatz and describing epilepsy as a network disease has brought great advances in its understanding [463–466]. The description of the human epileptic brain as a large-scale evolving epileptic brain network, derived from sampling the dynamics of observables in specific brain regions – associated with networks' vertices – and deducing the time-varying functional interactions between these brain regions with time-series-analysis techniques – associated with the networks edges – has been established as a successful approach [467]. Therefore, network analysis provides a powerful framework for understanding the interactions between different brain regions and how these interactions and the epileptic brain network changes over time. Through network analysis, prior studies were not only able to reveal that the seizure onset zone (SOZ) only plays a minor role in seizure dynamics [362, 468], but further that the temporal evolution of centrality values of certain network vertices – far-off the SOZ – hold vital information about impending seizures [421, 469].

Therefore, the authors of this publication conceived a research project with the larger aim to achieve a more general understanding of how the complex functional time-evolving brain network is altered prior to seizure. The authors achieved this through a more detailed characterisation of the involvement of specific network vertices in seizure generation, utilizing four complementary vertex centrality concepts [378]. Employing a sliding-window approach Timo Bröhl and Thorsten Rings derived the functional networks from multichannel, multiday intracranial electroencephalographic recordings of human electrical brain activity from a large number of people with epilepsy (cf. Chap. I B 4 and Chap. I D 4). For each window, the strengths of interaction between the dynamics of each pair of brain regions were derived using a bivariate time-series analysis technique, more precisely a phase-based estimator for edge weights, allowing to assign a weight to each edge in the respective functional network. Under the supervision of Timo Bröhl, Rieke Fruengel employed the different vertex centrality metrics to investigate the temporal evolution of each vertex's integration in the network, differentiating between pre-seizure and seizure-free periods. With the complementary and comprehensive information yielded by the different centrality concepts, the authors were able to trace changes in the evolving epileptic brain network specific to pre-seizure periods. While the authors observed, prior to seizure, almost all networks vertices to be, on average, increasingly interconnected within the network, they further hypothesized that this is not due to a single but multiple network mechanisms possibly underlying seizure generation.

Based on the observations of vertices that carry predictive information about impending seizures, and how the integration of these vertices changes prior to seizure, Timo Bröhl, proposed multiple different reconfiguration scenarios of the evolving large-scale epileptic brain network. In combination, these local and global network-altering mechanisms affect virtually all network constituents associated with various brain regions and functional connections between them.

Besides possible confounding influences regarding the distinction of seizure-free and pre-seizure periods, the effects of antiepileptic medication and other drugs, sleep deprivation, and infradian rhythms ($> 24$ h) [470–472], the authors further highlight that the high individuality of the subject-specific implantation schemes of electrodes, possible spatially oversampling of clinically deemed vital brain regions (SOZ), as well as spatially undersampling [469] of possibly important brain regions can lead to serve misinterpretations with regard to the network approach. This further stresses the need to reevaluate the concept of a SOZ, as well as the need to sufficiently sample the human epileptic brain. The authors proposed to further exhaust the capabilities of the network ansatz and to specifically investigate the role of edges in the involvement of specific mechanisms leading to seizure generation [377], as it already has been shown that edges also may carry information about impending seizures in the time-varying property of edges weights [421]. Investigating the integration of predictive vertices and of predictive edges in combination, as well as how this integration changes over time, may aid in advancing the proposed mechanisms involved in seizure generation or even facilitate the identification of new ones. This ultimately, may allow to paint a more comprehensive picture about alterations in the functional epileptic brain network specific to the generation of seizures, possibly involving only certain constituents or groups of such. In total, relating these results to the underlying anatomy and physiology could not only provide deeper insights into the generation of seizures but further hold vital implications about possible targeted treatment strategies [473–475], translating the network approach into clinical practice.

# VII Emergence of a tipping subnetwork during a critical transition in networked systems: A new avenue to extreme events

Timo Bröhl and Klaus Lehnertz

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To this day, various scientific fields are challenged with understanding and predicting critical transitions, which are unexpected and often irreversible shifts in a system's state or its dynamics. These transitions can culminate in extreme events with potentially disastrous consequences for the system and its environment. As many man-made and natural complex systems exhibit critical transitions and extreme events, studying these dynamical phenomena is of immense relevance. Critical transitions are largely observed to be emergent phenomena, where the collective system dynamics cannot be trivially inferred from properties and dynamics of its individual units. Yet, and despite decades of research, only modest advancements have been made in detecting, understanding and possibly predicting critical transitions and entailed extreme events [476–478]. This may possibly be due to a predominant focus on either specific subsystems or the system as a whole, largely dismissing the direct influence of time-varying relationships between the subsystems – ultimately constituting the networked complex system – and therefore neglecting vital characteristic of the emergent phenomena. In this paper, the authors shifted the focus from traditional approaches which concentrate on either global or unit-centric properties to a perspective that focuses on interactions between elementary units of complex networked systems to identify tipping elements [479] associated with the respective critical transition. To this end, Timo Bröhl investigated excitable complex networks and human epileptic brains, either of which are capable of self-generating critical transitions that result into extreme events, relating to complex phase synchronization phenomena.

The complex networked systems consisted of diffusively coupled FitzHugh-Nagumo oscillators [294, 295], with underlying complex, yet archetypical coupling topologies. The FitzHugh-Nagumo equation is a paradigmatic model for excitability with broad applicability in diverse scientific fields, ranging from engineering, over epidemiology, to cardiology and neuroscience [296, 480–482].

The investigated human epileptic brain networks resulted from multichannel, multiday intracranial electroencephalographic (EEG) recordings of electrical brain activity from more than 45 people with epilepsy.

Utilizing the network ansatz, Timo Bröhl derived time-evolving functional networks, associating vertices with the respective systems' units (single oscillators or sensors) and associating edges with interactions between these units, with the properties of the latter characterised from appropriate observables of the units' dynamics employing the mean phase coherence as a suitable estimator for the strength of the pair-wise interactions [218] (cf. Chap. I B 4 and Chap. I D 4).

In the toy models as well as in the natural system human brain, Timo Bröhl identified multiple tipping elements (vertices and/or edges), which generally are characterised by an abrupt shift in their respective state, associated with the critical transition. In this paper, tipping vertices and edges were associated with significant changes in their integration in the greater network when comparing critical transitions to normal dynamics. In order to assess this integration, Timo Bröhl employed several complementary centrality concepts for vertices [378, 483] and edges, partly introduced in earlier publications (cf. Chap. II and Chap. V). A networks constituent was hence deemed a tipping element, if any of the assessed centralities showed significant changes when comparing critical transitions to normal dynamics. The authors identified a large amount of tipping constituents in each of the investigated systems and therefore hypothesized about the presences of vital substructures introducing the concept of a tipping subnetwork. This subnetwork describes a connected network of exclusively tipping vertices and tipping edges. Timo Bröhl identified the presence of such a tipping subnetwork – containing most of the tipping constituents – in the large majority of the investigated systems.

The authors account the diversity in the relative sizes of the tipping and non-tipping subnetworks of the respective systems, to the different systems' dynamics, as – apart from toy models – access to their full spatial and temporal extend might be limited, especially in natural systems [176, 217, 394, 397] (cf. Chap. III).

Investigating the alteration of the tipping subnetwork in greater detail – via global and local network characteristics – the authors observed a rigidification of the tipping subnetwork. This indicated a possible diminished susceptibility of the tipping subnetwork to dynamics unrelated to the generation of extreme events. The authors hypothesized that this vital insight can help to isolate the mechanisms involved in the generation of critical transitions and extreme events.

The authors conclude that future online-detection and -characterisation of tipping subnetworks can ultimately allow the development of more refined mathematical models for critical transitions and time-series-analysis techniques that can aid to tackle the challenges associated with the detection, characterisation, and prediction of critical transitions and their entailed extreme events.

# VIII The time-evolving epileptic brain network: concepts, definitions, accomplishments, perspectives

Timo Bröhl, Thorsten Rings, Jan Pukropski, Randi von Wrede and Klaus Lehnertz.
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Epilepsy is one of the most common neurological disorders in the world, with a prevalence of about 1% [346, 484]. It poses a great burden on many intricate levels of affected people's lives, largely due to defining dynamical phenomena and their occurrence: epileptic seizures. Epileptic seizures hold life-changing implications for people with epilepsy and people close to them. From a physics perspective, epileptic seizures fit the definition of extreme events as rare, reoccurring, spontaneous, and large deviations from the brains regular dynamic, as they manifest as abnormal and excessive, synchronous neuronal activity in the brain [336]. The exhibition as well as the apparent unpredictable nature of epileptic seizures often has disastrous consequences, including risk of injuries, loss of autonomy, and psychosocial burdens [337–340]. Hence, understanding the emergence, propagation and cessation of epileptic seizures is rather crucial to deepening our understanding of the nature of epilepsy, which is crucial to develop novel and effective diagnostic approaches and treatment options.

Today, epilepsy is recognized as a complex network disorder affecting the brain across various spatial and temporal scales. This shift from viewing epileptic seizures as originating from a discrete cortical area in the brain to understanding it as a dynamical process on a widespread epileptic network, spanning lobes and hemispheres, has significantly aided in deepening our understanding of epilepsy as a disorder. In recent research, it is further considered that this complex epileptic network is not static but evolves in time. From a physics and also from a clinical perspective, this sparks the necessity for innovative and novel approaches to comprehensibly characterise (functional) time-evolving networks.

Therefore, in this review the authors presented an overview on and discussed the foundational concepts of network theory and critically assessed the current and most prominent recording techniques and analysis tools employed to derive and characterise the time-evolving human epileptic brain network.

Timo Bröhl provided an overview of concepts and metrics that allow to characterise network properties and internal organization ranging from the local [127, 140, 156, 164, 378], over intermediate [102, 127–129, 414, 485] to the global scale [104, 113, 115, 118, 122, 123, 486–490]. He further reviewed the state-of-the-art characterisation of time-evolving brain networks, including the investigation of temporal fluctuations in brain dynamics [422, 491], the identification of spontaneous or induced (patho-)physiologic changes and commonly used, yet controversially discussed, metrics and approaches for direct or indirect network comparison [73–76, 239, 240, 492].

The authors also summarized alternative approaches to investigating changes in the human epileptic brain network, including uni-, bi-, and multivariate time-series-analysis techniques [6, 196, 493–496]. They depicted how the time-evolving brain network changes during pre-seizure periods as well as during seizure-free periods, reporting on various results from different studies regarding specific reconfigurations and modifications of networks – together with their stability and robustness – (cf. Chapter VI) [61, 377, 421, 497–499]. Timo Bröhl depicted exemplary changes of the functional networks' path-structure prior to seizure in comparison to seizure-free periods, highlighting the formation of bottlenecks related to seizure generation. The authors underlined the possible implications of network alterations specific to certain dynamical phenomena, presenting research findings from different treatments of epilepsy, including antiseizure medication [500, 501], neuromodulation [502, 503], responsive neurostimulation [504] and vagus nerve stimulation [64, 505–508]

Lastly the authors reviewed conceptual issues, ranging from limitations in computational and mathematical models for epilepsy based on dynamical systems theory [509–512] and the network ansatz [513, 514] to general investigation of seizure-like extreme events [323, 446, 515–517], as well as different tipping [17, 518–520] and switching phenomena [521–529]. Further they presented (potential) translational issues of the network approach into clinical practice, differentiating between diagnosing epilepsy, choosing treatments and optimizing/monitoring therapies.

Overall, in this review the authors discussed and presented the general approach to describing epilepsy as a network disease via a large-scale, time-evolving epileptic brain network. Although this is a difficult task, advances of the last two decades have provided insights and progressed the field with various innovative tools of analysis. The review concluded that the current insights into the temporal evolution of the epileptic brain network hold significant promise for clinical application, advancing the state-of-the-art in epilepsy diagnosis and treatment, and further suggests that extending investigations into the temporal evolution of epileptic and other diseased brain networks, in comparison with non-affected brains and healthy brain dynamics, will be instrumental to further improve our understanding of epilepsy as a network disease.

# IX Conclusions and outlook

The omnipresence of complex dynamical systems in nature has significant implications for humans, as these systems' dynamics often shape the world around us. These dynamics range from synchronization phenomena [6] in coupled (non-linear) oscillators [530–534], in power grids [5, 8, 535–538], and in the human organism [66, 200, 539–541] to synchronization in complex networks, in general [7]; from spreading phenomena like rumours in social structures [542, 543], diverse information transport in socio-technical systems [10], epidemic outbreaks [175, 187, 190, 544, 545], to more general spreading processes on complex networks [546–548]; from critical transitions [285, 527, 549] in socio-economic structures like financial markets [550] or social networks [476], critical transitions in diseases [284, 551–553] or in the climate system [232, 433, 554–558], to critical transitions that can entail extreme events [22], such as rogue waves [559, 560] and floods [561, 562], heat waves [563–565] and droughts [270, 566], over solar flares [262, 567], large-scale blackouts in power grids [278, 428, 568–570], cardiac arrhythmias [298, 571], fatal heart failure [284], migraine attacks [286], as well as epileptic seizures in the human brain [409, 572].

The vast variety of different dynamical phenomena exhibited by complex systems has vital impact and potentially pose substantial risks not only to the systems themselves but also to their environments. Given these often catastrophic consequences, expanding our understanding of underlying processes of specific dynamical phenomena is crucial for developing approaches to predict and understand their occurrence, and mitigate or potentially prevent their outcomes. However, due to the remarkable complexity of these systems [573–575], this task remains far from trivial and further necessitates the advancement of new tools and concepts to address associated challenges.

With the premise that a complex dynamical system can viewed as a networked system of elementary units, a promising approach to studying such complex systems is the network ansatz, which has been successfully applied to the wide range of spatially extended complex dynamical systems mentioned above. For many of the dynamical phenomena observed in nature, the respective system's collective dynamics is thought to emerge from the intricate interplay of interactions between the dynamics of the system's (elementary) units. In this thesis, we substantially extended the network ansatz and the time-evolving functional network approach to describe and study complex systems by constructing static and/or time-evolving (functional) networks, where vertices represent the system's elementary units, and edges denote properties of interactions between these units, estimated with time-series analysis techniques [62, 72]. While so-far, the network ansatz has primarily focused on understanding the dynamics of individual units or the network as a whole, we proposed that shifting the focus to the explicit interactions between the system's units – represented by the network edges – and their intricate interplay – alterations of subnetworks – can offer valuable insights into emergent phenomena, such as critical transitions and extreme events. Beside the advances such a shift in perspective might hold in the described network ansatz, we hypothesized that this novel perspective will be of great value for any conceivable extensions of the network ansatz. The above mentioned systems exhibit a range of emergent phenomena that are critical to various scientific fields, their investigation further holds potential for adaptation of gained knowledge and of developed methodologies to other complex dynamical systems in nature. Nevertheless, the inherent complexity of such systems presents numerous challenges, from assessing the systems' individual units' dynamics to accounting for external influences and time-varying interactions [573, 576].

It is the concept of centrality, and our fundamental yet innovative adaptation of established as well as our introduction of novel centrality metrics (cf. Chap. II), that is key in this constituent-centric and therefore also edge-centric analysis. Centrality metrics are utilized to quantify the importance of network constituents – both, vertices and edges – based on their roles or embedding in the overall network [140]. The combination of results yielded by multiple centrality metrics, allows to investigate the integration of constituents within the network in a comprehensive manner.

Generally, the large majority of centrality metrics can be divided in two groups, either focusing on aspects of the networks' path-structures or aspects of the networks' degree and strength distributions, which furthermore consider these aspects in either a global (e.g. betweenness and eigenvector centrality) or local (e.g. closeness centrality) manner. In this context, it is important to note, that prior to the publication of the nearest-neighbor centrality [154] no edge centrality metric assessed the local and strength-based properties of edges. The nearest-neighbor centrality is a straightforward extensions of the concept of a vertex's degree or strength, as it assess the importance of edges based on the strength of interactions of adjacent edges and the connected vertices' strengths [114]. Applied to (static) paradigmatic models, as well as social networks, this new centrality revealed additional and complementary insights into structural and also functional aspects of the respective system, highlighting local and global bottleneck structures, possibly relating to potential dynamical phenomena these system are able to exhibit. In this context, our findings further suggest that generally edge-centric investigations of complex networks are of vital use when studying spreading phenomena such as rumour or epidemic spreading [546, 577–580], for which path-based or more global centrality metrics show limited applicability. We explored the relevance of this edge-centric approach in investigating excitable complex dynamical system (such as the human (epileptic) brain) and their emergent dynamical phenomena, namely extreme events (such as epileptic seizures). By examining time-evolving functional networks prior to these events we identified key interactions between the elementary units of the systems. Overall, our results suggest that the edge-centric approach and particularly the combination of various complementing centrality metrics, not only significantly enhance our understanding of extreme-event-specific spatial-temporal dynamics and further allow to elucidate mechanisms involved in critical transitions and extreme events in complex systems.

### Edge centrality concepts

By now there is an upsurge of novel edge centrality metrics [581–588] which may, at least to a certain extent, has been triggered by preliminary research to this thesis [155]. Nevertheless, it is conceivable that centrality metrics may be advanced under a perspective apart from path- or strength-based concepts. Although a complementing character of the majority of the various centrality metrics has been shown [158, 586, 589–592], there is neither a trivial way to actually compare how different centrality metrics assess the roles of constituents in the network, nor how a specific centrality metric assesses the role of one constituent compared to an other constituent in the network. The reliability and clarity of centrality values can be at times uncertain, partly due to potential numerical issues, which can raise questions about when centrality values can be considered distinct or equivalent. Hence, it is of vital importance to develop metrics and mathematical concepts that allow to estimate or measure the reliability of centrality values. Although ranking centrality values, as commonly employed in prior studies [156, 157, 593] as well as in this thesis, facilitates easier comparisons between the assessments of different centrality metrics, the aforementioned issues translate to the question of when two elements should be assigned the same rank, or whether assigning identical ranks is even valid given the research context. Therefore, depending on the system under investigation and the respective research question, the applicability of centrality metrics may still be limited. This necessitates the development of alternative concepts, whether it be a constituent's integration in mesoscopic structures in the network, similarity aspects between network constituents or even more algebraic approaches to a networks adjacency matrix.

Furthermore, while the temporal evolution of centrality values can provide crucial insights into a system's dynamics and behaviour [594–597] (see also Chap. IV, VI, and VII), most centrality metrics do not explicitly account for time or the evolving nature of a network. Hence, especially when studying complex dynamical systems, a centrality metric that considers a constituent's role based on how its integration within the network evolves over time could be particularly valuable.

Apart from changes in local or global characteristics to assess changes of time-evolving networks, direct comparisons between (snapshot) networks is conceptually challenging [77]. While it is generally conceivable to define a (Euclidean) distance [598], or covariance and correlation [599] measurements for adjacency matrices, as of now no suitable mathematical concepts are available to easily deduce such metrics. Further, these metrics would likely require crucial constraints regarding a network's size, in terms of present vertices and edges [239]. In example, evaluating the change resulting from the presence of specific vertex/edge in one network and the absence of this vertex/edge in an other network is highly non-trivial.

### Field data investigations

One of the more fundamental and persistent challenges in studying real-world networked complex systems is the limited knowledge about the system's elementary units and their interactions [36, 43, 56, 62]. Yet despite these limitations, the network approach remains a powerful tool for gaining insights into the dynamics of such systems [487]. By employing time-series-analysis techniques, we estimated interaction properties between elementary units (associated with network edges) from data captured from the dynamics of the elementary units (associated with network vertices). However, the absence of a one-fits-all time-series-analysis technique, along with the challenges of noisy field data and appropriate sensor placement, often leads to over- or undersampling of the investigated system [394, 397, 400, 402], resulting in misinterpretations of network characteristics [193, 217] and ultimately the system's properties. It is a vital yet difficult undertaking to identify potentially superfluous network constituents [399, 401, 404, 405].

As part of this thesis we developed a

perturbation-based approach to tackle these issues, leveraging the concept of centrality to identify potentially redundant or essential constituents within the network (cf. Chap. III). With centrality metrics assessing the importance of a network constituents via their integration in the larger network, here we are able to estimate a constituents role in the network in a rather holistic and comprehensive manner. Therefore, targeting single network constituents, by cloning or removing them, ultimately leads to an overall minuscule alteration of the network from a structural perspective, with perturbation-induced changes in the centrality values of all other network constituents, reflecting either a vital or superfluous character of the targeted constituent, depending on whether the centrality values changed in a great extend or not at all. Our method demonstrated that paradigmatic network models can contain superfluous constituents depending on the network's topology, size, and edge density, with far less potentially superfluous constituents observed in complete and regular networks than in more complex topologies, such as small-world and scale-free networks.

We further hypothesized that our perturbation-based approach, and potential extensions of it, can help to gain decisive insights about relevant network constituents (vertices and edges) in real-world complex networked systems which can possibly relate to essential or redundant elements in the system or highlight sampling issues. This can hold vital implications about entailed investigations of real-world-systems and their dynamics, as the systems' distinct topological makeup can influence interpretations of network properties independent of the systems' dynamical aspects.

It is often not straightforward which interaction properties – such as strength, direction, or functional form – between elementary units in a system should be represented by network edges and their attributes, as this largely depends on the specific research question and the system being studied. The perturbation-based approach, combined with complementary centrality metrics, may help to compensate the absence of a universal null model for edges in a network, or even contribute to the development of such a model.

Another rather substantial issue when studying real-world dynamical systems, is the influence of various natural and endogenous cycles. Their influences have been shown to be reflected in measurements of the dynamics of systems' elements, ranging from resonance phenomena caused by traffic on bridges that led to their failure [600], fluctuations in animal population in the wilderness [601], over energy demand dynamics in power networks [602], to general response patterns of non-oscillatory cardiac conducting tissues [603–605], and EEG measurements of the human brain [422, 606, 607]). In employing the network ansatz to describe the time-evolving complex system human brain, we demonstrated how such rhythms impacted the temporal evolution of functional networks (cf. Chap. IV). Our investigation of long-term EEG-recordings revealed vital and fundamental subnetworks within the time-evolving functional network and how biological rhythms influence the centrality of specific network constituents, shedding new light on the concept of the extensively investigated resting-state network [423], as well as fundamental processes such as memory consolidation [424, 425], consolidation of spatial and visual information, as well as overall and general ongoing brain activities. Our findings emphasize the importance of considering endogenous cycles when studying time-evolving functional brain networks and highlight the potential for centrality metrics to reveal key insights into both physiologic and diseased brain dynamics. In principal, a transfer of this methodology, and also its entailed issues, is imaginable for any time-evolving network that describes a complex dynamical system, and might aid to reveal dependencies of the system's dynamics and suitable observables in regard to endogenous and exogenous driving forces [608]. This could include investigation of pandemic spreading in social networks [609–611], predator-prey relationships in food-web networks [612], and the respective influences of day-and-night, weekly or even seasonal cycles.

The recognition that such cycles can significantly influence real-world systems and their dynamics motivates extending or even adapting the time-evolving network approach. Currently, when studying complex time-evolving systems, the network ansatz is typically used in combination with a sliding-window approach to generate snapshot networks. However, each snapshot network, in isolation, represents a static structure without an inherent time-dependency. Moreover, in many natural systems, the coupling topology can undergo intrinsic changes, such as those caused by the motion of the system's elementary units [613]. This phenomenon is observed in various contexts, including social networks [614–617], mobile communication networks [370, 618, 619], power transmission systems [620], and the human brain [491, 621].

Developing a time-dependent network framework, where the temporal evolution of both the network's properties and its constituents' characteristics are directly embedded in its mathematical structure, may be crucial for fully capturing the dynamic aspects of certain complex systems that are otherwise missed due to the conceptual limitations of the current network ansatz. In the absence of mathematical models to describe a time-dependent network, conceptual approaches that map time series to ordinal patterns [622] using ordinal time-series-analysis techniques [623, 624] hold promising potential to advance toward a time-dependent network framework. Although this approach and its resulting abstraction leads to a loss of information, it captures essential aspects of the temporal structure of the underlying system dynamics as well as the properties of interactions between coupled units, and already holds great potential to shed light on spatial-temporal dynamics in complex dynamical systems.

### Critical transitions and extreme events

Utilizing the time-evolving network ansatz [72] with the aim to improve our understanding and characterisation of complex dynamical phenomena, and specifically emergent phenomena such as critical transitions and extreme events, we studied networks of excitable units of FitzHugh-Nagumo oscillators with different coupling topologies – archetypical for many networked dynamical systems in nature. With prior research having revealed vital aspects of the mechanisms associated with the generation of extreme events [322, 450], involving a critical mass of oscillators to be in an excited dynamical state, it remained to be investigated how the residual oscillators got recruited into this state, which ultimately constitutes the emergent character of such extreme events. Therefore, employing complementary centrality metrics and proposing a network decomposition technique based on edge centralities, we revealed that this recruitment, independent of the underlying coupling topology, was facilitated by certain (sets of) edges in the time-evolving functional networks (cf. Chap. V). These edges were typically classified as either highly important or entirely unimportant, based on the corresponding centrality metric. We hence concluded that especially certain interactions between a systems' units – associated with specific network edges – are decisively involved in the generation of extreme events, which further harbours great potential for possible control of a system and its dynamics [443, 444] by targeting these specific interactions or even distinct interaction pathways. So-called link removal is commonly employed concept [625], which describes the perturbation of certain edges in a network to control the dynamics of the respective system. This approach has been explored across a wide range of applications, including spreading phenomena [399, 408, 626, 627], changes in network robustness [107, 628], synchronization in power networks [629], and even the neutralization of terror networks [630]. Similarly, the removal of specific pathways in a network is imaginable, yet requires methods to detect crucial pathways. So far, most methods proposed have a vertex-specific focus, aiming at detecting communities [631], motifs [131, 632], or other constituent groups through network decompositions [137, 633]. There is a notable lack of analogous methods for identifying edge-specific structures, such as pathways. Utilizing or directly expanding the concept of centrality with a shift in perspective from the local to the mesoscopic network scale, in combinations with bottom-up or top-down decomposition concepts, presents a promising avenue for developing new metrics to identify crucial mesoscopic structures, including pathways.

Interestingly, the edges identified as involved in the generation of extreme events were found to have no direct equivalent in the underlying coupling topology (cf. Chap. V). Differences between functional networks and their corresponding coupling structures have been widely observed across various systems [35, 46, 79, 634, 635], yet these discrepancies are notoriously challenging to explain, particularly when estimating interaction properties. In many natural systems, it is often unclear whether the coupled subsystems interact exclusively in pairwise fashion, whether these interactions are transitive, or if higher-order interactions need to be taken into account. Hence, often times a direct mapping between edges in a functional network and the pairwise interactions in the respective coupling structures may not be suitable, as it is conceivable, that one ore multiple units are mediating the interaction between two other units for which no direct interaction is present. Ultimately, this can lead to severe misinterpretations of interaction properties or the presence of not only superfluous but potentially incorrect edges. A commonly applied approach to address these challenges is the concept of partialization, with respective estimators [208, 209, 636–644] for interaction properties considered robust against transitivity. However, it remains to be investigated whether these estimators, and extensions of such, face limitations similar to those identified in other non-partialized estimators for determining the properties of interactions, particularly when investigating interactions in larger networks ($\gg 20$ vertices). The proposed perturbation-based approach, along with possible adaptations and the concept of edge centrality, can significantly contribute to addressing these challenges, enhancing our understanding – or facilitate the development of techniques to do so – of the relationship between interactions and the coupling of local and global dynamics in complex systems.

Building on the novel insights into the importance of local network characteristics and the role of specific network constituents, as outlined in Chap. V, we investigated in greater detail critical transitions and extreme events in complex networked systems of diffusively coupled FitzHugh-Nagumo oscillators, as well as in the human epileptic brain (epilepsy as a network disease reviewed in Chap. VIII), with our focus sharpened on the intricate interplay of network constituents that carry predictive information about impending extreme events, such as epileptic seizures.

In association with the concept of tipping elements [479], we identified multiple tipping vertices and edges, whose tipping nature is associated with significant changes in their integration in the greater network, when comparing critical transitions to normal dynamics. We employed the concept of centrality, combining complementary centrality metrics to gain a detailed understanding of the integration of network constituents and the changes in these integrations over time. While previous research largely focused on the detection of certain network vertices that carried predictive information about impending extreme events [645], in this thesis we also were able to specify edges with homologous characteristics, carrying predictive information about impending extreme events, not only in model systems of coupled FitzHugh-Nagumo oscillators but also in time-evolving functional networks of epileptic brains. We identified an extensive amount of tipping constituents, whose majority formed a large connected tipping subnetwork. The respective tipping subnetwork showed vital differences in its global and local network characteristics during critical transitions compared to normal dynamics, pointing to an overall rigidification of this tipping subnetwork during a critical transition. We concluded that this rigidification could indicate a reduced susceptibility of the tipping subnetwork to dynamics unrelated to the mechanisms driving or generating extreme events. This could further enable a more focused and isolated study of the tipping subnetwork within the context of critical transitions, potentially providing deeper insights into the dynamics leading up to these events. For the time-evolving functional brain networks, identified tipping vertices and edges were primarily associated with brain regions – or interactions between such – far off the clinically defined brain are exhibiting earliest signs of seizure activity. With the observed alterations of global as well as local network characteristics of time-evolving functional brain networks, we proposed major reconfigurations scenarios affecting virtually all network constituents associated with various interacting brain regions (cf. Chap. VI). In the context of time-evolving functional brain networks, we hypothesized that these results, set in relation to underlying anatomical and physiological aspects, could elucidate our understanding of the generation of epileptic seizures, which harbours great potential to develop improved prediction, mitigation or possibly even prevention strategies. Overall, we concluded that a detailed study of tipping subnetworks and the major reconfigurations scenarios of the time-evolving functional networks can substantially contribute to the development of refined and possibly novel mathematical models for critical transitions in general, as well as time-series-analysis techniques that allow to tackle persistent challenges encountered in approaches to detection, characterisation and prediction of critical transitions and entailed extreme events.

Although many dynamics of complex systems found in nature can be considered as emergent phenomena, the scale at which this emergent behaviour is most pronounced is neither always clear nor trivially inferable. The identification of vital mesoscopic structures, likely playing a crucial role in the generation of dynamics in the investigated complex dynamical systems here, highlights the potential advantages – and maybe even the necessity – of developing more refined methods for uncovering specific mesoscopic structures in complex networks. While an edge-centric focus is essential to comprehend emergent properties of system dynamics, a too narrow and local perspective may miss decisive and potentially inseparable relations between multiple elementary units in the system [646–653]. These challenges could be addressed by developing and utilizing direct approaches to uncover mesoscopic structures, or by rethinking how interaction properties are estimated, refining existing and developing novel time-series-analysis techniques. This shift in perspective would move from focusing on pairwise interactions to higher-order interactions [654, 655], and potentially even group interactions at the mesoscopic level [656, 657], potentially offering a more comprehensive view of complex system dynamics.

Wrongfully applied or interpreted time-series-analysis techniques can have direct consequences on drawn conclusions about the system and its dynamics and therefore lead to severe misinterpretations [658]. It is crucial to develop methods and tools that can robustly estimate the accuracy and reliability of results generated by different time-series analysis techniques. Surrogate testing is a statistical method designed to assess the significance of findings in time-series analysis. In theory, it helps determine whether observed relationships in real-world data are meaningful or simply the result of randomness. Although there have been certain advancements in surrogate techniques [192], particularly for evaluating the strength of interactions [246, 252, 659, 660], methods that test the reliability of both the strength and direction of an interaction – or even coupling functions [661] – are still in the early stages of development.

### From dyadic to polyadic time-dependent interaction networks

The large majority of complex systems in nature not only operate on multiple temporal and spatial scales but also function as elements within a larger, interconnected system of systems. This includes human organisms as a whole [540, 541, 662], with neuron activity operating in the microseconds, the heart beating in the order of seconds, the gastrointestinal tract operating in the span of minutes to hours, or growth cycles (e.g. of hair) lasting up to multiple years; the climate systems [43], with interactions and teleconnections between see surface temperature and heat weaves [663], extreme rainfalls [430, 664] and atmospheric processes, as well as as the climate change as a whole [665–667]

Studying these systems can greatly benefit from an extension of the network ansatz to one that emphasizes a *network of networks* [373, 668, 669], with the purpose to bridge temporal and spatial scales. In this context, interactions between networks or their constituent elements may yield crucial insights into the interplay between structure, function, and overall dynamics. Over the past decade, several approaches have been proposed to tackle the challenges of describing and investigating such systems of systems. Notably, multiplex [670–673] and multilayer networks [410, 411, 674, 675] have been applied successfully to explore properties and dynamics in complex systems, including food webs [676], epidemic spreading networks [677], photonic resonator networks [678], financial networks [679], the brain [680], and even the human organism as a whole [540, 541, 681]. However, many of the established metrics and concepts that assess the properties of individual networks have limited applicability when extended to a network of networks. This highlights the need for further research to refine existing metrics and develop novel ones that account for the interactions between different network layers. Here also an edge-centric approach may provide a more nuanced understanding of interlayer edges that connect networks, allowing for a detailed characterisation of interactions between elements across layers [682, 683].

Additionally, an important and potentially transformative extension of the network paradigm is to consider edges that connect multiple vertices, leading to the framework of *hypergraphs* [92, 684, 685]. Most available time-series-analysis techniques either assume that the systems being studied are (approximately) stationary and that interactions remain stable and persistent throughout the observation period or necessitate the use of a sliding-window approach, which assumes approximate stationarity within each time window. In this context, the hypergraph approach becomes particularly relevant for non-stationary systems. Further, it may be especially useful when investigating systems where the assumption of exclusive pairwise interactions between elementary units does not hold, or where multiple forms of coupling coexist [686, 687]. The interplay of multiple different coupling forms is possibly essential for the emergence of complex dynamical phenomena. Describing higher-dimensional simplices (with dimensions $\geq 2$) by evaluating properties of *higher-order interactions* – transient or non-transitive interactions between multiple units of a system – has garnered significant interest. In recent years, this approach has seen substantial conceptual [688–690] and applied research across various scientific fields [544, 655, 691–698]. It remains uncertain whether a single approach can be universally applicable and well suited to characterise all relevant properties of (transient) interactions among non-stationary systems.

One of the most promising yet complex and challenging frontiers is the integration of the time-dependent network approach into the hypergraph ansatz, an area of development that has yet to mature fully [699–702]. Here edges and their properties could be hypothesized to encapsulate the time-evolving properties of different couplings and their respective properties, possible leading not only the definition of time-evolving or time-dependent multi-edges, but further different types of edges in the network. We conjecture that for this framework especially edge-centric metrics and also fundamental advancements and developments presented in this thesis will be of vital significance to shed light on the intricate interplay of different time-evolving interactions and their properties, aiding to expedite our understanding of complex emergent dynamical phenomena, under the scope of time-dependent hypergraphs.

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# Auxiliaries

The contents of this thesis were thoroughly discussed with Professor Dr. Klaus Lehnertz and Dr. Thorsten Ring throughout the course of my doctoral studies. The majority of the software used for numerical simulations, data analysis, and visualization was developed in Python 2 and Python 3, utilizing packages such as *numpy*, *scipy*, *pandas*, *matplotlib*, and *graph-tool*, among others. For image processing, the open-source software *Inkscape* was employed. I hereby declare that this thesis is the result of my independent work, conducted in accordance with the principles of good scientific practice. Only the sources and resources explicitly cited and referenced have been used. All verbatim and non-verbatim quotations from other works have been properly identified and attributed in line with academic citation guidelines. This thesis has not been submitted, in whole or in part, for any previous examination or degree

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# Appendix

The accepted manuscripts for the articles included in this cumulative thesis are appended in the following.

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# A straightforward edge centrality concept derived from generalizing degree and strength

Timo Bröhl[1,2] & Klaus Lehnertz[1,2,3]✉

**Vertex degree—the number of edges that are incident to a vertex—is a fundamental concept in network theory. It is the historically first and conceptually simplest centrality concept to rate the importance of a vertex for a network's structure and dynamics. Unlike many other centrality concepts, for which joint metrics have been proposed for both vertices and edges, by now there is no concept for an edge centrality analogous to vertex degree. Here, we propose such a concept—termed nearest-neighbor edge centrality—and demonstrate its suitability for a non-redundant identification of central edges in paradigmatic network models as well as in real-world networks from various scientific domains.**

Complex network approaches have been repeatedly shown to provide deeper insights into structure and dynamics of spatially extended complex systems in diverse areas of science[1–9]. In many natural and man-made networked systems, access to the underlying coupling structure may be restricted or even impossible. Nevertheless, in such cases can the system be described by an interaction network with vertices representing subsystems or elementary units and edges representing interactions between them. This ansatz has been successfully applied e.g. in the study of (functional) brain networks[10], climate networks[11,12], protein-protein interactions[13], gene interactions[14], plant-pollinator interactions[15,16], food-webs[17], or communication and social networks[18,19].

In order to further improve understanding and control of interaction networks, the identification of key network constituents and a characterization of their importance for a network's structure and dynamics is highly relevant[20–27]. There are different concepts and a growing number of metrics—such as centralities—that allow one to characterize the role of network vertices for structure and dynamics[28]. There are by now, however, only a few metrics for edge centrality. Many of them center around the concept of betweenness centrality[29–35], other make use of the concept of bridging[36–39] or are based on the spectrum of the network's Laplacian[40,41]. We have recently introduced modifications of closeness and eigenvector centrality concepts for vertices to those for edges and demonstrated that these edge centralities provide additional information about the network constituents for various topologies[42].

The aforementioned joint centrality concepts for vertices and edges can be classified as path-based (betweenness centrality $\mathcal{C}^{\mathrm{B}}$ and closeness centrality $\mathcal{C}^{\mathrm{C}}$) or degree/strength-based (eigenvector centrality $\mathcal{C}^{\mathrm{E}}$). Interestingly, there is by now no edge centrality concept analogous to the historically first and conceptually simplest centrality[43], namely vertex degree centrality, which is defined as the number of edges incident upon a vertex. In case of a weighted network, the corresponding vertex strength centrality[44,45] is defined as the sum of weights of these edges. Here, we propose such an analogous edge centrality concept, which we termed nearest-neighbor edge centrality $\mathcal{C}^{\mathrm{N}}$. Using various paradigmatic network models, we illustrate this edge centrality concept and investigate possible relationships to the other aforementioned edge centrality concepts. We will then apply the novel concept to identify important edges in a commonly used benchmark model in social network analysis, in a commuter network as well as in evolving epileptic brain networks.

## Results and discussions

**Joint centrality concepts for vertices and edges.** Let us briefly recall and discuss the most commonly used joint centrality concepts (betweenness centrality $\mathcal{C}^{\mathrm{B}}$, closeness centrality $\mathcal{C}^{\mathrm{C}}$, and eigenvector centrality $\mathcal{C}^{\mathrm{E}}$) for vertices and edges. We here consider binary or weighted, undirected and connected networks that consist of sets of vertices $\mathcal{V}$ and edges $\mathcal{E}$, with $V = |\mathcal{V}|$ and $E = |\mathcal{E}|$ denoting the number of vertices and edges, respectively.

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We do not consider self-loops or parallel edges. Centrality concepts that are based on shortest paths require the definition of “length” $d_{ij}$ of a path between vertices $i$ and $j$. In a binary network, the length $d_{ij}$ of a shortest path P between vertices $i$ and $j$ is the number of edges along this path. We define $d_{ii} := 0$ as we do not consider self-loops. In a weighted network, since an edge weight represents the strength of a connection between two vertices, we consider a path to be shorter the stronger the connections along this path are. Consequently, we relate $d_{ij}$ of path P between vertices $i$ and $j$ to the sum of the inverse weights of edges along this path[43]. A shortest path can be defined as the path between two vertices for which the sum of the inverse weights of edges along this path is minimal[42].

**Betweenness centrality.** With betweenness centrality $\mathcal{C}^{\mathrm{B}}$, a network constituent is the more central the more shortest paths pass through this constituent. Vertex/edge betweenness centrality (of vertex/edge $k$) can be defined as[30,46,47]

$$\mathcal{C}^{\mathrm{B}}_{\mathrm{v,e}}(k) = \frac{2}{F}\sum_{i\neq j}\frac{q_{ij}(k)}{G_{ij}}, \tag{1}$$

where $k \in \{1,\ldots,V\}$, resp. $k \in \{1,\ldots,E\}$, $\left\{i,j\right\} \in \{1,\ldots,V\}$, $q_{ij}(k)$ is the number of shortest paths between vertices $i$ and $j$ running through vertex/edge $k$, and $G_{ij}$ is the total number of shortest paths between vertices $i$ and $j$. The normalization factor is $F = (V-1)(V-2)$ in case of vertices and $F = V(V-1)$ in case of edges.

With this definition (Eq. 1), $\mathcal{C}^{\mathrm{B}}_{\mathrm{v}}$ may assign disproportionately large centrality values to vertices with an arbitrary and possible very low degree (at least 2) and a neighboring vertex of degree 1, as every shortest path between the degree-1 vertex and every other vertex in the network has to traverse the vertex adjacent to the degree-1 vertex. In a similar manner will an edge between a degree-1 vertex and the adjacent vertex be assigned a disproportionately large centrality value. Apart from the normalization factor $F$, $\mathcal{C}^{\mathrm{B}}_{\mathrm{v}}$ and $\mathcal{C}^{\mathrm{B}}_{\mathrm{e}}$ are equally defined and for the latter, one also considers—contrary to intuition—the shortest paths between all vertex pairs and not between all possible pairs of edges in the network.

This of course has also the advantage of reducing computation time drastically when calculating edge betweenness centrality. Furthermore, $\mathcal{C}^{\mathrm{B}}$ does not directly depend on the distribution of edge weights in the network. It finds wide application and the concept yields distinct and non-redundant information about a network in comparison with the other centrality concepts.

**Closeness centrality.** With closeness centrality $\mathcal{C}^{\mathrm{C}}$, a constituent is the more central the shorter the paths that connect this constituent to every other reachable constituent of the same type. Closeness centrality of vertex $k$ is defined as[48]:

$$\mathcal{C}^{\mathrm{C}}_{\mathrm{v}}(k) = \frac{V-1}{\sum_i d_{ik}}, \tag{2}$$

with $(k,i) \in \{1,\ldots,V\}$. Closeness centrality of edge $k$ between vertices $a$ and $b$ can the be defined as[42]:

$$\begin{aligned}\mathcal{C}^{\mathrm{C}}_{\mathrm{e}}(k) &= \frac{E-1}{\sum_i (d_{ia}+d_{ib})} = \frac{E-1}{\frac{1}{\mathcal{C}^{\mathrm{C}}_{\mathrm{v}}(a)}+\frac{1}{\mathcal{C}^{\mathrm{C}}_{\mathrm{v}}(b)}}\\ &= (E-1)\frac{\mathcal{C}^{\mathrm{C}}_{\mathrm{v}}(a)\mathcal{C}^{\mathrm{C}}_{\mathrm{v}}(b)}{\mathcal{C}^{\mathrm{C}}_{\mathrm{v}}(a)+\mathcal{C}^{\mathrm{C}}_{\mathrm{v}}(b)},\end{aligned} \tag{3}$$

with $k \in \{1,\ldots,E\}$ and $(a,b,i) \in \{1,\ldots,V\}$.

Closeness centrality is the only centrality concept that directly depends on the path structure in a network as well as on the distribution of edge weights. The concept mostly finds application in network studies that model some kind of information flow. Nevertheless, due to its definition, $\mathcal{C}^{\mathrm{C}}$ lacks applicability regarding networks with disconnected components[49,50].

**Eigenvector centrality.** With eigenvector centrality $\mathcal{C}^{\mathrm{E}}$, a network constituent is central if its adjacent constituents of the same type are also central. Eigenvector centrality $\mathcal{C}^{\mathrm{E}}$ of vertex[51] or edge[42] $k$ is defined as the $k$th entry of the eigenvector $\mathbf{v}$ corresponding to the dominant eigenvalue $\lambda_{\max}$ of matrix $\mathbf{M}$, which can be derived from the eigenvector equation $\mathbf{M}\mathbf{v} = \lambda\mathbf{v}$ using the power iteration method:

$$\mathcal{C}^{\mathrm{E}}_{\mathrm{v,e}}(k) = \frac{1}{\lambda_{\max}}\sum_l M_{kl}\,\mathcal{C}^{\mathrm{E}}_{\mathrm{v,e}}(l). \tag{4}$$

In case of vertices, $\{k,l\} \in \mathcal{V}$ and $\mathbf{M}$ denotes the adjacency matrix $\mathbf{A}^{(\mathrm{v})} \in \{0,1\}^{V\times V}$ of a binary network, with $A^{(\mathrm{v})}_{kl} = 1$ if there is an edge between vertices $k$ and $l$, and 0 otherwise. In case of a weighted network, $\mathbf{M}$ denotes the weight matrix $\mathbf{W}^{(\mathrm{v})} \in \mathbb{R}_{+}^{V\times V}$, with $W^{(\mathrm{v})}_{kl}$ denoting the weight of an edge between vertices $k$ and $l$. In a binary network, the degree $\kappa_k$ of vertex $k$ is defined as the number of its neighbors ($\kappa_k := \sum_j A^{(\mathrm{v})}_{kj}$). Its weighted counterpart is the strength $s_k := \sum_j W^{(\mathrm{v})}_{kj}$. We define $A^{(\mathrm{v})}_{kk} := 0\,\forall\, k$ and $W^{(\mathrm{v})}_{kk} := 0\,\forall\, k$ with $k \in \{1,\ldots,V\}$.

In case of edges, $\{k,l\} \in \mathcal{E}$ and $\mathbf{M}$ denotes the edge adjacency matrix $\mathbf{A}^{(\mathrm{e})} \in \{0,1\}^{E\times E}$ of a binary network, with $A^{(\mathrm{e})}_{kl} = 1$ if edges $k$ and $l$ are connected to a same vertex, and 0 otherwise. In case of a weighted network, $\mathbf{M}$ denotes the weight matrix $\mathbf{W}^{(\mathrm{e})} \in \mathbb{R}_{+}^{E\times E}$ whose entries $W^{(\mathrm{e})}_{kl}$ are assigned the average weight of edges $k$ and $l$ if these edges are connected to a same vertex, and 0 otherwise. As above, we define $A^{(e)}_{kk} := 0 \, \forall \, k$ and $W^{(e)}_{kk} := 0 \, \forall \, k$ with $k \in \{1, \ldots, E\}$.

Eigenvector centrality also presents with some limitations. Much like for closeness centrality, $\mathcal{C}^{\mathrm{E}}$ lacks applicability to networks with disconnected components. Depending on the network structure, one might encounter weight distributions that decrease exponentially with increasing degree. In this case most of the constituents will be assigned centrality values close to zero and, therefore, the importance of the constituents may insufficiently be quantified.

However, compared to $\mathcal{C}^{\mathrm{B}}$ and $\mathcal{C}^{\mathrm{C}}$, $\mathcal{C}^{\mathrm{E}}$ is the only centrality concept based on spectral properties of the (weighted) adjacency matrix. While the path-based concepts $\mathcal{C}^{\mathrm{B}}$ and $\mathcal{C}^{\mathrm{C}}$ only indirectly consider the network as a whole to identify shortest paths, the strength-based concept $\mathcal{C}^{\mathrm{E}}$ considers the structure of the total network in a gradual but direct manner.

**Nearest-neighbor edge centrality.** With the concept of strength centrality, a vertex is the more central the stronger the connections to adjacent vertices are. The strength (or strength centrality) of vertex $k$ reads:

$$\mathcal{C}^{\mathrm{S}}_{\mathrm{v}}(k) = s_k = \sum_{j} W^{(\mathrm{v})}_{kj}, \tag{5}$$

with $(k, j) \in \{1, \ldots, V\}$ and the weight matrix element $W^{(\mathrm{v})}_{kj}$ (see above). Analogously the degree $\mathcal{C}^{\mathrm{D}}_{\mathrm{v}}(k)$ of a vertex $k$ is defined as sum of adjacent vertices to vertex $k$. The concept on its own is limited to the total level of involvement of a vertex in the network and does not take into account intrinsic properties of a vertex (as there exist no such properties). Instead it considers an intrinsic property of edges connected to a vertex, namely the edge weights. Moreover, it does not take into account the number of adjacent vertices, which has been described as a main feature in Freeman's centrality metrics[43]. Aiming to derive a comparably simple and straightforward definition of edge centrality, one naively could use the edge weight itself. This would give, however, no perspective of the edges' role in a network, as an edge weight has no direct relation to the network's structure. Furthermore, such an edge centrality would not represent an analogue to the degree/strength of a vertex. To achieve just that, an edge centrality would have to depend on intrinsic properties of the two vertices connected by an edge. As there is no intrinsic vertex property, we here resort to the vertices' degrees/strengths to derive a 'strength'-related centrality concept for edges. We consider an edge to be more central the larger its weight and the more similar and the higher the strengths of the vertices which are connected by that edge. For a binary network, we define nearest-neighbor edge centrality $\mathcal{C}^{\mathrm{N}}_{\mathrm{e}}$ of an edge $k$ between vertices $a$ and $b$ as:

$$\mathcal{C}^{\mathrm{N}}_{\mathrm{e}}(k) = \frac{\mathcal{C}^{\mathrm{D}}_{\mathrm{v}}(a) + \mathcal{C}^{\mathrm{D}}_{\mathrm{v}}(b) - 2}{|\mathcal{C}^{\mathrm{D}}_{\mathrm{v}}(a) - \mathcal{C}^{\mathrm{D}}_{\mathrm{v}}(b)| + 1}\ , \tag{6}$$

where $k \in \{1, \ldots, E\}$ and $(a, b) \in \{1, \ldots, V\}$.

Analogously, for a weighted network we define:

$$\mathcal{C}^{\mathrm{N}}_{\mathrm{e}}(k) = \frac{\mathcal{C}^{\mathrm{S}}_{\mathrm{v}}(a) + \mathcal{C}^{\mathrm{S}}_{\mathrm{v}}(b) - 2w_k}{|\mathcal{C}^{\mathrm{S}}_{\mathrm{v}}(a) - \mathcal{C}^{\mathrm{S}}_{\mathrm{v}}(b)| + 1}\ w_k, \tag{7}$$

where $k \in \{1, \ldots, E\}$ and $(a, b) \in \{1, \ldots, V\}$, and $w_k$ denotes the weight of edge $k$ connecting vertices $a$ and $b$.

The numerator of the fraction of Eq. 7 (Eq. 6) captures the 'strength' ('degree') of the edge, as it effectively describes the sum of weights of adjacent edges (sum of adjacent edges)—edges that share a vertex. The denominator represents the difference of the strengths of the two vertices connected by the edge. Hence, an edge is the more central the larger the weights of its adjacent edges are and the more symmetrical these edge weights are distributed between the two vertices. We therefore define an edge to be more central if it is connected to vertices that are both strongly connected in the network than an edge that is connected to one very strongly connected vertex and one weakly connected vertex (e.g., an edge as one of many edges connected to a hub). Furthermore, the weight of the edge itself contributes to its centrality. This compensates for the fact that even overall weakly connected vertices, with possibly high degrees but low strength, can also be connected by a highly central edge. Overall, nearest-neighbor edge centrality is independent of the network's topology and size and is solely based on local network characteristics. An additional normalization factor ($\frac{1}{2(V-2)}$) can be considered when aiming at a comparison with other edge centrality concepts, since established edge centrality concepts (e.g., $\mathcal{C}^{\mathrm{B}}_{\mathrm{e}}$) are also normalized with respect to the total number of vertices.

**Comparison with other edge centralities.** We begin by addressing the question whether our introduced centrality concept provides non-redundant information about edges in weighted networks when compared to other edge centrality concepts. To this end, we investigate paradigmatic network models with different sizes $V \in \{50, 100, 200\}$, perform correlation analyses of edge ranks obtained with the different centrality metrics, and investigate the normalized rank difference $\delta = (\mathrm{rank}^{\mathrm{N}}(\Omega) - \mathrm{rank}^{\bullet}(\Omega))/E = (1 - \mathrm{rank}^{\bullet}(\Omega))/E$, where $\Omega$ denotes the most important edge as identified with $\mathcal{C}^{\mathrm{N}}_{\mathrm{e}}$, and $\bullet \in \{\mathrm{B}, \mathrm{C}, \mathrm{E}\}$. If the nearest-neighbor centrality concept identifies the same edge as most important (rank 1) as the centrality concept we compare it to (betweenness, closeness, eigenvector) , $\delta$ will vanish.

We consider small-world networks[52] (with rewiring probabilities $p_r \in \{0.01, 0.1, 0.2, 0.3\}$), scale-free networks[53] (parameter of attachment $m \in \{4, 6, 10\}$), random networks[54,55] (with edge creation probabilities $p_c \in \{0.3, 0.5, 0.7\}$), and fully connected networks, for each of which we generated 100 realizations. For each realization of these weighted networks, we draw weights from some distribution, and in the case of equal centrality

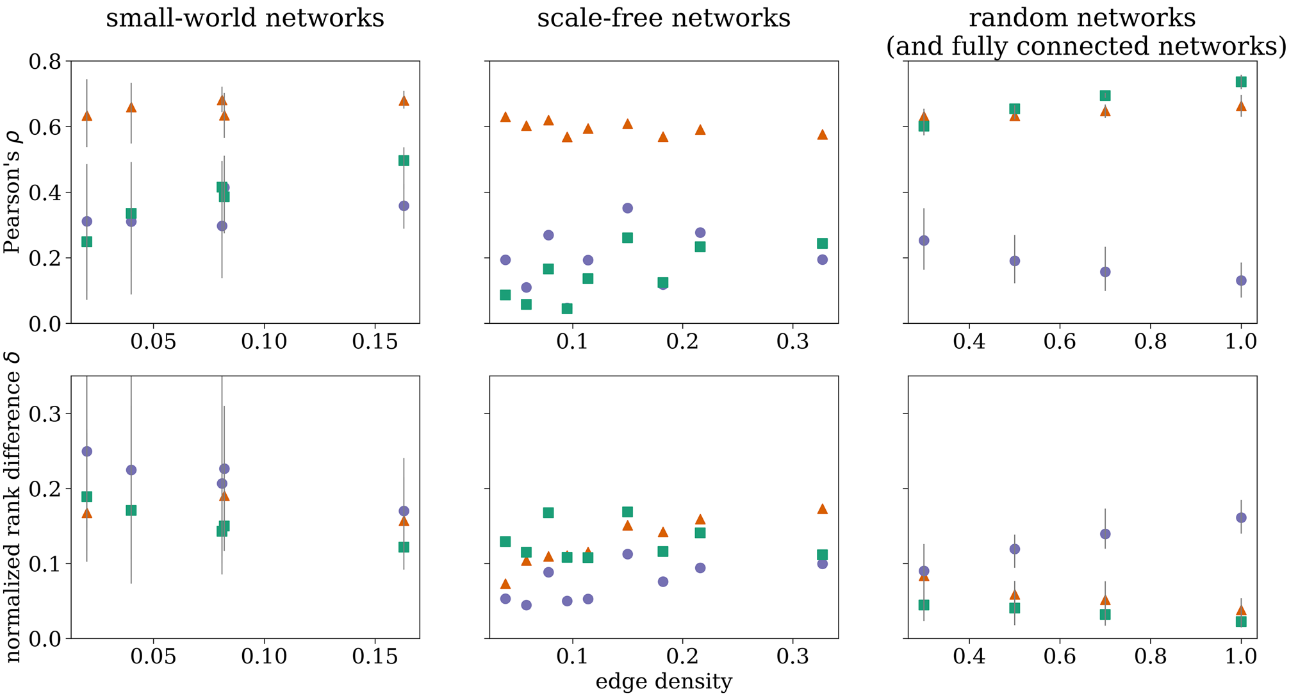

**Figure 1.** Nearest-neighbor edge centrality provides non-redundant information about edges in paradigmatic network models. Correlations (Pearson's $\rho$) of edge ranks (top) and normalized rank differences $\delta$ (bottom) obtained with the different centrality metrics for the investigated network topologies and edge densities. Means and ranges (lengths of error bars) obtained from 100 realizations of the network topologies. Different colors encode pairs of edge centralities used for correlation analyses and analysis of normalized rank differences: orange triangle—($\mathcal{C}_\mathrm{e}^\mathrm{N}$,$\mathcal{C}_\mathrm{e}^\mathrm{B}$), purple circle—($\mathcal{C}_\mathrm{e}^\mathrm{N}$,$\mathcal{C}_\mathrm{e}^\mathrm{C}$), and green square—($\mathcal{C}_\mathrm{e}^\mathrm{N}$,$\mathcal{C}_\mathrm{e}^\mathrm{E}$). Note that for scale-free networks error bars are smaller than symbol size.

values (for a given centrality concept), we rank in the order of appearance. All networks are undirected and connected, contain no self-loops and no multiple edges.

Figure 1 summarizes our findings for the aforementioned analyses with weights drawn from the uniform distribution $\mathcal{U}(0,1)$. We obtained similar findings for weights drawn from other distributions (Gaussian, Gumbel with different locations of the mode). In general, we observe a wide range of correlation values ($\rho \in [0.0, 0.8]$) and these vary for different network topology as well as for different edge densities. We find overall highest correlation values ($0.7 < \rho \leq 0.8$) for a comparison with $\mathcal{C}_\mathrm{e}^\mathrm{E}$ which, however, is to be expected since both these edge centralities strongly depend on the weight distribution of the edges that are adjacent to the edge under investigation. For small-world and scale-free networks, we observe highest correlation values when comparing with $\mathcal{C}_\mathrm{e}^\mathrm{B}$, which may be related to path structure properties that are characteristic for these topologies: shortcuts and bottlenecks. In case of the most important edge as identified with $\mathcal{C}_\mathrm{e}^\mathrm{N}$, we observe $\mathcal{C}_\mathrm{e}^\mathrm{C}$ and $\mathcal{C}_\mathrm{e}^\mathrm{E}$ to yield more similar ranks than $\mathcal{C}_\mathrm{e}^\mathrm{B}$. Based on the definitions of $\mathcal{C}_\mathrm{e}^\mathrm{N}$, $\mathcal{C}_\mathrm{e}^\mathrm{C}$ and $\mathcal{C}_\mathrm{e}^\mathrm{E}$, similarities—especially in identifying the most important edge—are to be expected. Nevertheless, the most important edge as identified with $\mathcal{C}_\mathrm{e}^\mathrm{N}$ does not coincide with the most important edge as identified with the other centrality concepts. Furthermore, we observe very few concordances between central edges (up to rank 10) as identified with $\mathcal{C}_\mathrm{e}^\mathrm{N}$ and those identified with one of the other three centralities (data not shown). In case of small-world networks and weights drawn from a Gumbel distribution with a location of the mode around 0.2, we observe highest concordance. Here, in approx. 37% of realisations, $\mathcal{C}_\mathrm{e}^\mathrm{N}$ and $\mathcal{C}_\mathrm{e}^\mathrm{E}$ identify the same most important edge. However, over all realizations, the concordance rate between any edge from the top 10 ranking based on $\mathcal{C}_\mathrm{e}^\mathrm{N}$ with any edge from the top 10 ranking based on $\mathcal{C}_\mathrm{e}^\mathrm{B}$, $\mathcal{C}_\mathrm{e}^\mathrm{C}$ or $\mathcal{C}_\mathrm{e}^\mathrm{E}$ is less or equal 5%. Taken together, central edges identified with $\mathcal{C}_\mathrm{e}^\mathrm{N}$ are not assigned the same rank when identified with $\mathcal{C}_\mathrm{e}^\mathrm{B}$, $\mathcal{C}_\mathrm{e}^\mathrm{E}$ or $\mathcal{C}_\mathrm{e}^\mathrm{C}$, and are also not assigned a rank close to it.

Summarizing these findings, we conclude our novel centrality concept to provide non-redundant information about network edges when compared to other edge centrality concepts.

**Identifying important edges in real-world networks.** We next demonstrate the utility of the proposed edge centrality concept for understanding which edges are important in real-world networks. We here focus on Zachary's karate club network[56], which is a commonly used benchmark model in social network analysis, on a commuter network[57–59], and on evolving epileptic brain networks[60–62]. We regard an edge with the highest centrality value as most important and the one with the lowest centrality value as least important. In the case of equal centrality values, we rank in order of appearance.

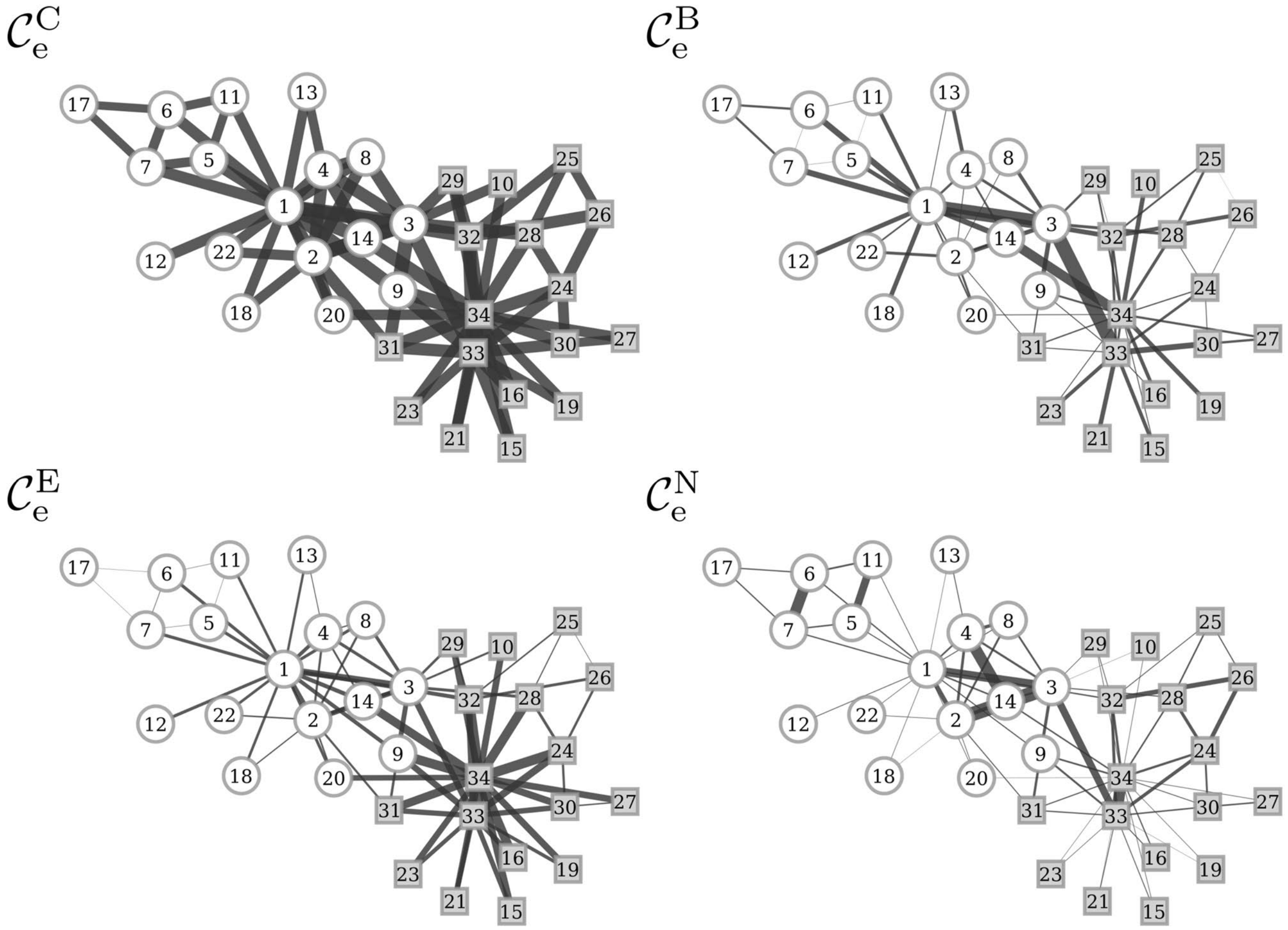

**Figure 2.** Key interactions in Zachary's karate club network. Interactions identified with different edge centrality concepts (edge closeness centrality $\mathcal{C}_e^C$; edge eigenvector centrality $\mathcal{C}_e^E$; edge betweenness centrality $\mathcal{C}_e^B$; nearest-neighbor edge centrality $\mathcal{C}_e^N$). Edge importance is encoded as line thickness and numbered vertices represent the members of the club. The two factions into which the club split during the course of the study are indicated by circles [the club instructor's group (vertex 1)] and squares [the club administrator's group (vertex 34)].

**Zachary's karate club network.** The network consists of 34 persons (vertices) whose interactions (78 weighted edges) have been carefully investigated over a period of three years. Shortly after Zachary finished his research, the karate club split into two smaller groups. This was due to a conflict and disagreements between the club's instructor (vertex 1) and administrator (vertex 34) regarding the prices of karate lessons. This ultimately resulted in the instructor's leaving and launching a new club, taking about a half of the original club's members with him. The fission was to 97 % correctly predicted by Zachary based on his observations regarding social interactions.

The conflict between the two individuals (instructor and administrator) was carried out on a much larger social structure, with each individual trying to win as many students for their cause. As neither the instructor nor the administrator necessarily had intensive relationships to each and every student, individual opinion formation was based on much more complex social structure modeled by the network. Furthermore, the instructor and the administrator had no direct interactions with each other and an exchange of information between them relied on close intermediaries. Word of mouth, popular students, or specific relationships (bottlenecks) might be of vital importance in this context. Thus it is essential to identify key interactions between individuals that very possibly enabled the observed fission within the club. Figure 2 depicts these key interactions that we identified with different edge centrality concepts.

With edge closeness centrality $\mathcal{C}_e^C$, we obtained a very narrow distribution of centrality values, which does not allow a visual identification of key interactions. This can be generally explained by the fact that any vertex in this rather small network is comparably close to every other vertex.

With edge eigenvector centrality $\mathcal{C}_e^E$, we identify edges with the highest centrality values to connect vertices 33 and 34 (the administrator and a close student of his) with many other vertices. Other arguably important individuals, represented by vertices 1, 3, 9 and 14, are also connected via some few high-centrality edges, however, much less than the ones observed around the hubs (i.e., vertices 33 and 34). Eigenvector centrality is closely related to strength centrality and becomes almost indistinguishable from the latter in case of small networks. Hence, it can be expected to observe key interactions as the high-centrality edges that connect the high-degree/

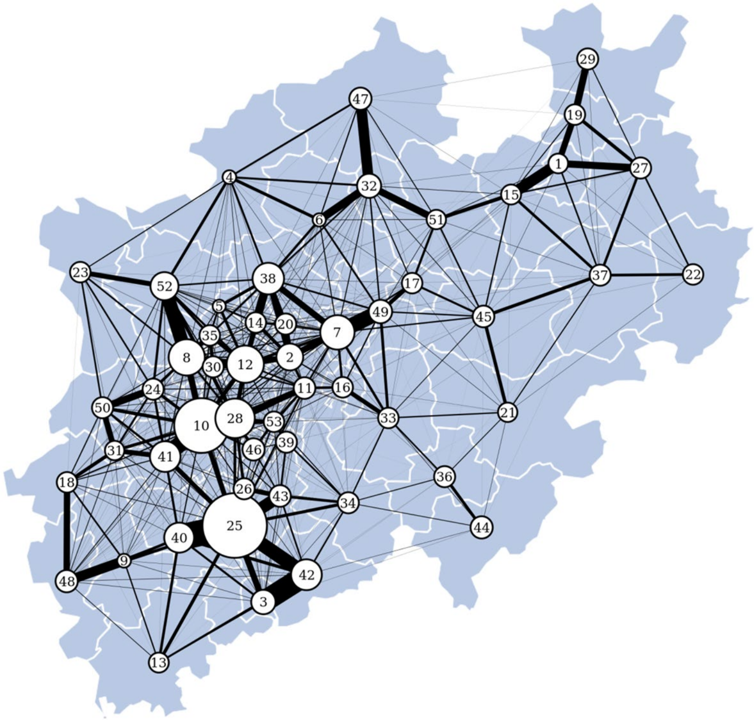

**Figure 3.** Commuter traffic network of North Rhine-Westphalia (NRW). Numbered vertices represent the rural and urban districts in NRW. Size of vertices represents their respective strength and thickness of edges represents the amount of commuter traffic between them.

high-strength vertices (1, 33, and 34) or as those that connect other vertices (namely vertices 3, 9, and 14) to the aforementioned vertices.

With edge betweenness centrality $\mathcal{C}_e^B$, many edges with comparably high centrality values connect vertex 1 (the instructor) to other vertices. Edges with highest centrality values, however, connect vertices 1 and 3, 3 and 33, as well as vertices 34 and 14. This can easily be understood since betweenness centrality is well suited to identify bottlenecks in a network. The aforementioned high-centrality edges represent some of the very few key interactions between the two parts of the network that resulted from the fission.

With nearest-neighbor edge centrality $\mathcal{C}_e^N$, we expect edges to reflect key interactions if they very strongly connect vertices that are equally densely integrated in the network and possibly in the two smaller groups of the network. These edges can be regarded as 'local' bottlenecks, possibly also coinciding with 'global' bottlenecks. Those local bottlenecks are edges that connect vertices 6 and 7, 5 and 11, as well as vertices 4 and 14. These edges are located in the sub-network centered around the instructor. Edges connecting vertices 1, 2, and 33 with vertex 3 can be associated with a more global bottleneck, which in part could also be identified with $\mathcal{C}_e^B$. The edge connecting vertices 2 and 3 has not been identified as important with $\mathcal{C}_e^B$, but appears to be most important using $\mathcal{C}_e^N$. This edge is to be associated with a larger bottleneck structure, being the path from vertex 2 to vertex 33, traversing vertex 3. Hence, vertices 2, 3, and 33 appear to be the main mediators between the club's instructor and administrator.

The fact that $\mathcal{C}_e^N$ highlights both, local and global bottlenecks in the karate club network distinguishes it from $\mathcal{C}_e^B$. We conjecture that $\mathcal{C}_e^N$ can aid in an improved characterization of the path structure in complex networks.

## Commuter network of the German state North Rhine-Westphalia.

The most populous state in Germany is North Rhine-Westphalia (NRW) with approx. 18 million inhabitants living on an area of more than 34,000 square kilometers. In addition to the German city-states, NRW is the most densely populated state, and commuter traffic within NRW is enormous[63]. Studying the network of commuter traffic can greatly aid to improve, e.g. understanding and control of spreading processes[57,59,64–69]. As a most recent example, we mention the spread of the corona virus SARS-CoV-2, with the urban district Heinsberg being one of the pandemic's origins in Germany.

For our analyses, we take the rural and urban districts in NRW as vertices of the commuter traffic network (Fig. 3). We consider an edge to exist between two vertices if commuter traffic between them was recorded, and the edge weight equals the average number of commuters traveling between two vertices on a day in 2017.

Figure 4 summarizes our findings that we obtained from applying the edge centrality concepts to identify important commuter connections. Similar to Zachary's karate club network, $\mathcal{C}_e^C$ does not highlight any specific connections since the distribution of edge weights is rather narrow. With $\mathcal{C}_e^B$, we observe a path between the north-east and south-west of NRW to be most important. It traverses geo-economically centers and population-dense districts, such as vertices 32 (Muenster), 12 (Essen), 10 (Dusseldorf) and 25 (Cologne). Interestingly

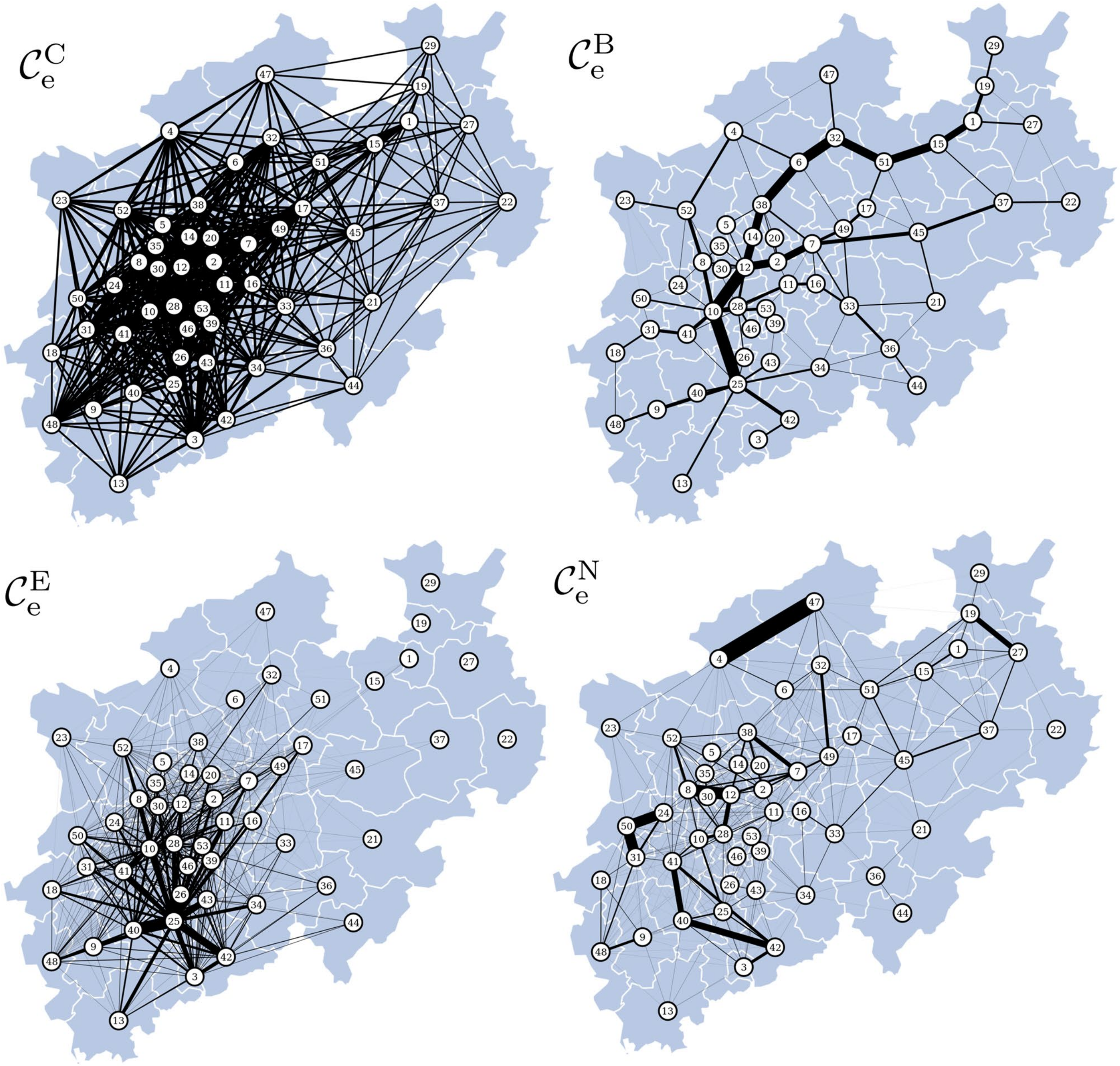

**Figure 4.** Key connections in the commuter traffic network of North Rhine-Westphalia (NRW). Connections identified with different edge centrality concepts (edge closeness centrality $\mathcal{C}_{\mathrm{e}}^{\mathrm{C}}$; edge eigenvector centrality $\mathcal{C}_{\mathrm{e}}^{\mathrm{E}}$; edge betweenness centrality $\mathcal{C}_{\mathrm{e}}^{\mathrm{B}}$; nearest-neighbor edge centrality $\mathcal{C}_{\mathrm{e}}^{\mathrm{N}}$). Numbered vertices represent the rural and urban districts in NRW and edges indicate commuter traffic between them. Edge importance is encoded as line thickness.

enough and even though spatially close, neither of these urban districts share a common border. The identified important edges, however, spatially traverse approximately one other district and therefore would generally not be considered as long-range connections.

With $\mathcal{C}_{\mathrm{e}}^{\mathrm{E}}$, particularly edges connecting to vertex 25 (Cologne) are highlighted. This is to be expected, as Cologne—besides being the most densely populated city in NRW—also records the highest commuter volume in NRW.

With $\mathcal{C}_{\mathrm{e}}^{\mathrm{N}}$, we observe edges to be important that are far off the expected commuter centers of NRW, namely the population-dense districts like vertex 25 (Cologne) as well as vertices in the Ruhr area. Certain peripheral edges (near the borders of NRW) are identified as important: for example, the edge connecting vertices 47 (Steinfurt) and 4 (Borken). These two urban districts do neither have a large population density nor a high commuter volume. The commuter traffic between them, however, is comparably large so that these two districts could be interpreted as one large district. Similar observations can me made for edges that connect vertices 50 (Viersen), 31 (Moenchengladbach) and 24 (Krefeld), vertices 40 (Rhein-Erft Kreis), 41 (Rhein-Kreis Neuss) and 42 (Rhein-Sieg Kreis), as well as for the edge that connects vertices 8 (Duisburg) and 12 (Essen) and the edge that connects vertices 19 (Herford) and 27 (Olpe).

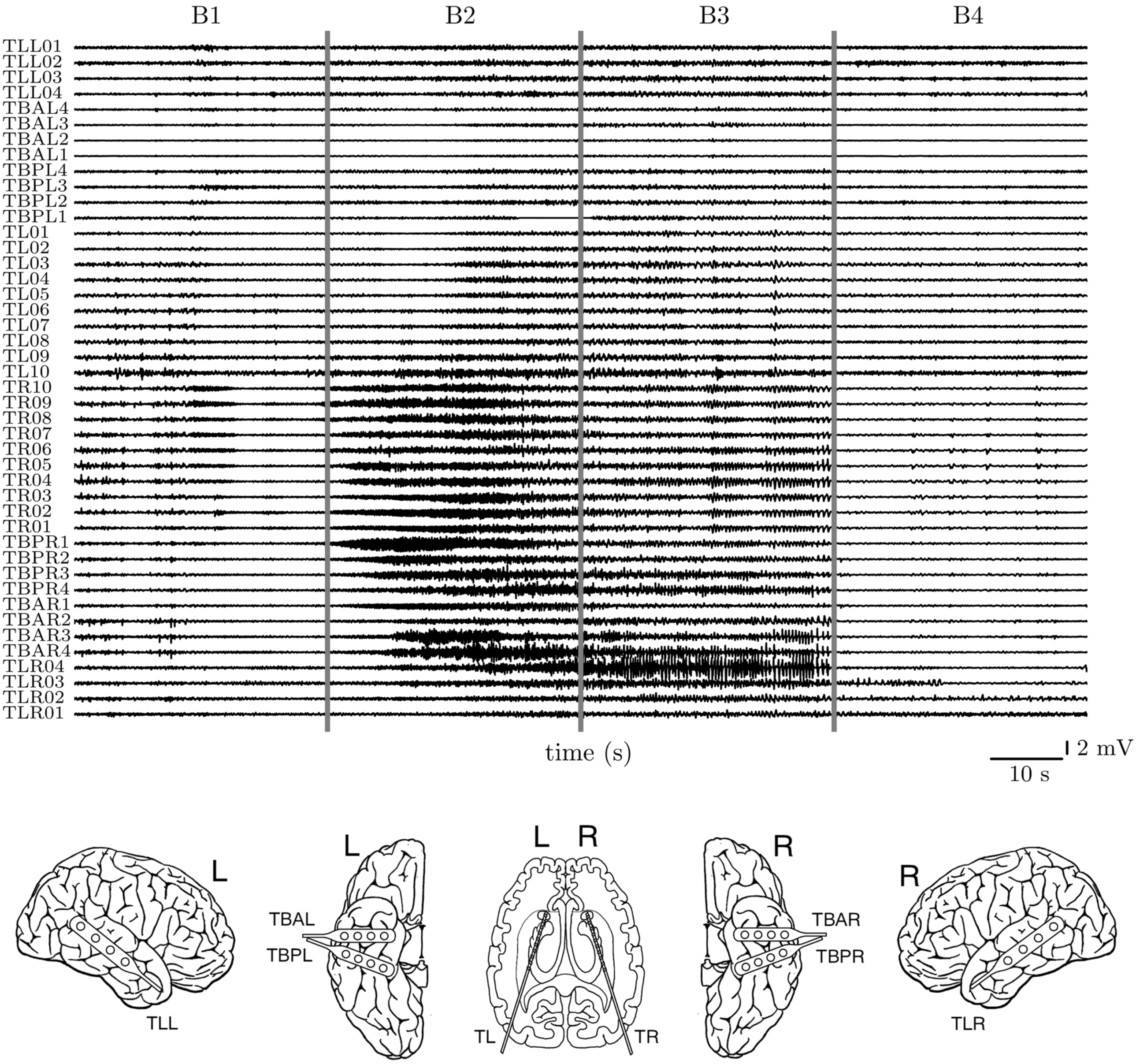

**Figure 5.** Brain dynamics during an epileptic seizure Top: invasive electroencephalographic recording of a seizure from the left (upper half) and right brain hemisphere (lower half). Block B1 indicates the pre-seizure phase; blocks B2 and B3 indicate the first and second half of the seizure (electroencephalographic seizure onset and ending determined automatically[70]); block B4 indicates the post-seizure phase. Bottom: schematics of sensors placed over the left and right temporal-lateral and temporal-basal neocortex and of bilateral intrahippocampal sensors.

**Evolving functional brain networks during an epileptic seizure.** Epilepsy is widely accepted as a large-scale network disease of the human brain[8,71], and it is of utmost importance to not only identify central network vertices and characterize their dynamics but also to identify and characterize central edges in evolving functional brain networks. An improved characterization of time-dependent changes of centrality of network constituents could advance understanding of seizure generation, spread, and termination as well as could aid in the development of novel treatment options.

Here, we re-analyze evolving functional brain networks[42] that were derived from multichannel electroencephalographic (EEG) data recorded from a subject with epilepsy prior to, during, and after a focal-onset seizure (see Fig. 5). The subject had signed informed consent that the clinical data might be used and published for research purposes. The study protocol had been approved by the ethics committee of the University of Bonn and is accordance with the tenets of the Declaration of Helsinki.

Briefly, the EEG data were recorded from sensors placed on the cortex and within relevant brain structures during the presurgical evaluation of the subject's medically uncontrollable epilepsy. Evolving weighted functional brain networks were derived by associating vertices with the sampled brain regions (sensors) and edges represent the time-varying strength of interactions between pairs of brain regions. For the latter, a sliding-window approach

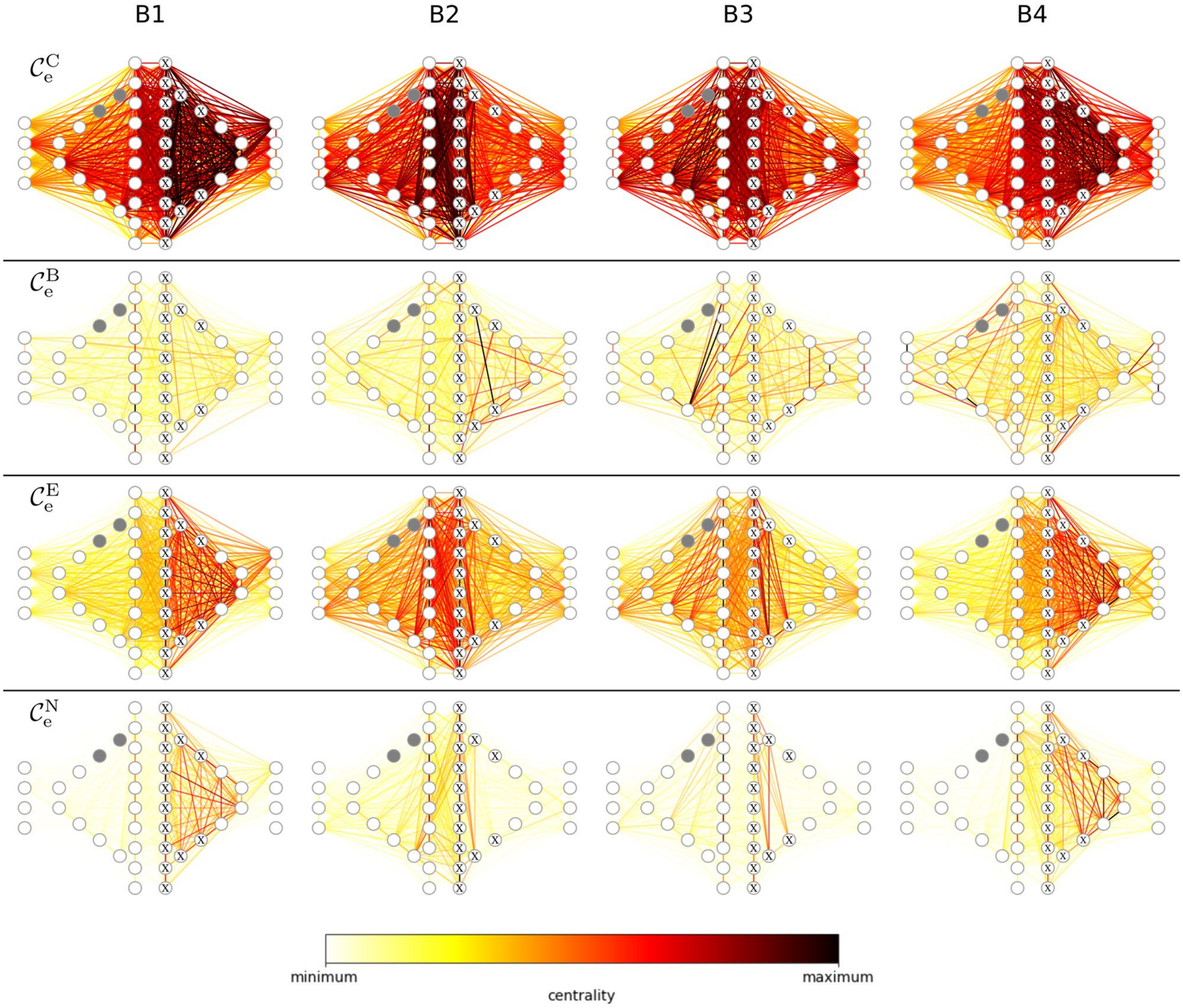

**Figure 6.** Key interactions in evolving functional brain networks during an epileptic seizure. Interactions identified with different edge centrality concepts (edge closeness centrality $\mathcal{C}_e^C$; edge eigenvector centrality $\mathcal{C}_e^E$; edge betweenness centrality $\mathcal{C}_e^B$; nearest-neighbor edge centrality $\mathcal{C}_e^N$). Vertices and edges projected onto a schematics of implanted sensors shown in Fig. 5. Edge color encodes normalized mean centrality values for each block (B1, · · ·, B4). Vertices marked with 'x' record from the clinically defined seizure onset zone, and grey-colored vertices indicate EEG reference sensors (not included in analyses).

was pursued (consecutive non-overlapping windows of 2.5 s duration each; corresponding to 500 data points) to calculate—in a time-resolved manner—the mean phase coherence $R$[72], which is an established data-driven method for studying time-variant changes in phase synchronization in EEG time series. $R$ is confined to the unit interval ($R = 1$ indicates fully synchronized systems) and is taken as an estimate for the strength of interaction between a pair of brain regions. We refer the reader to Ref.[42] for further details.

In Fig. 6, we present our findings that we obtained from investigating edge centrality in the temporal sequence of the weighted snapshot networks. Since centrality in such networks can vary strongly over time[60,73,74], we partition the recording into four blocks (B1, · · ·, B4) of equal duration. Each block contains the data from 13 consecutive snapshot networks and in the following, we report aggregated centrality values for each block.

For the evolving functional brain networks prior to and after the seizure (blocks B1 and B4), three of the four employed edge centrality concepts—namely $\mathcal{C}_e^C$, $\mathcal{C}_e^E$, and $\mathcal{C}_e^N$—yield qualitative similar findings. Edges connecting vertices related to the right brain hemisphere and particularly those that connect to vertices associated with the clinically defined seizure onset zone (located in the right brain hemisphere) excel with noticeably larger centrality values than edges connecting vertices related to the left hemisphere as well as than edges connecting vertices in both hemispheres. As with the other investigated real-world networks, we observe a rather peaked distribution of $\mathcal{C}_e^C$ values. Hence the differentiation between hemispheres is not as distinct as with $\mathcal{C}_e^E$ or $\mathcal{C}_e^N$. With $\mathcal{C}_e^B$, we observe only few edges with large centrality values. Prior to the seizure (block B1), these edges are confined to the left brain hemisphere and to a large extent connect vertices that face the seizure onset zone. After the seizure (block B4), $\mathcal{C}_e^B$ highlights some edges in the left and right brain hemisphere.

During the first half of the seizure (block B2), all concepts indicate high-centrality edges to connect vertices in the left and in the right brain hemisphere and particularly vertices associated with the seizure onset zone as well as its homologous regions in the opposite brain hemisphere. $\mathcal{C}_e^C$ (and to a lesser extent also $\mathcal{C}_e^E$) additionally highlights a larger number of high-centrality interhemispheric edges that dilutes during the second half of the seizure (block B3). In contrast, with $\mathcal{C}_e^B$ the amount of high-centrality interhemispheric edges even slightly increases during B3. $\mathcal{C}_e^N$ indicates high-centrality edges to connect nearby vertices in homologous regions in the opposite brain hemisphere during B3.

Although the employed centrality concepts mostly indicate different edges as important (as expected), our findings point to widespread, even interhemispheric interactions as highly relevant for seizure dynamics. Although these findings need to be validated on a larger database, they indicate that characterizing important edges in evolving functional brain networks can help to improve understanding of the complicated spatial-temporal dynamics of epileptic seizures.

## Conclusion

We introduced a novel edge centrality concept—nearest-neighbor edge centrality—that is defined in an analogous manner as the well-known and widely used vertex degree/strength centrality. By investigating possible relationships to other edge centralities (such as edge betweenness, edge closeness, and edge eigenvector centrality[30,42,46]) we could demonstrate the suitability of nearest-neighbor edge centrality for an identification of central edges in paradigmatic network models as well as in real-world networks from various scientific domains. Despite the expected conceptual similarities to either of the compared edge centralities, nearest-neighbor edge centrality provides additional and non-redundant information about the role edges play in a network. Moreover, nearest neighbor edge centrality can be computed much faster (up to a factor of 10) than path-based or edge-adjacency-matrix-based edge centralities, since—by definition—it depends solely on the distribution of vertex strengths.

Generally, we consider our nearest-neighbor edge centrality concept to be advantageous particularly in those situations were path-based or more global centrality concepts may have limited significance, e.g., for investigations of local spreading phenomena. The joint use of vertex degree/strength centrality and nearest-neighbor edge centrality could help to improve understanding the role vertices and edges play in the larger networks and thus to gain deeper insights into central but local network phenomena.

The definition of the nearest-neighbor edge centrality as proposed here is based on vertex strength and it thus allows investigations of undirected and weighted networks. Nevertheless, extensions to directed as well as to binary networks, to networks of networks[75], multigraphs[76], or hypergraphs[77] can be achieved taking into account the total or in- and out-degree/strength of vertices. Such extensions might even lead to a modification of existing or formulation of novel concepts and measures that—in addition to degree-/strength distribution—also include the distribution of nearest-neighbor edge centrality values, to achieve a more complete characterization of a network.

Eventually, and with an eye on the analysis of real-world data, we expect new insights, by revisiting, extending and modifying network-based time-series analysis techniques such as visibility graphs[78]. We are confident that the nearest-neighbor edge centrality concept will help to improve characterization of networks through a data-driven identification of important edges.

## Data availability

The data for this work was taken from the following sources: The Zachary's karate club network data was taken from The KONECT Project (http://konect.cc/). The commuter traffic data was taken from data collected by the Statistisches Landesamt NRW (https://www.landesdatenbank.nrw.de/link/statistikTabellen/19321—Statistik: 19321). The rest of the data may be made available, upon request to the authors.

## Code availability

The code for the analysis was programmed using standard libraries in Python. All the calculations can be reproduced with the equations provided in the main text. Even so, the code used here is available upon request to the authors.

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# A perturbation-based approach to identifying potentially superfluous network constituents

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## ABSTRACT

Constructing networks from empirical time-series data is often faced with the as yet unsolved issue of how to avoid potentially superfluous network constituents. Such constituents can result, e.g., from spatial and temporal oversampling of the system's dynamics, and neglecting them can lead to severe misinterpretations of network characteristics ranging from global to local scale. We derive a perturbation-based method to identify potentially superfluous network constituents that makes use of vertex and edge centrality concepts. We investigate the suitability of our approach through analyses of weighted small-world, scale-free, random, and complete networks.

**Understanding complex dynamical systems such as climate and brain profits from the network approach. Deriving networks from measurements of the systems' dynamics, however, can lead to spurious indications of network properties, depending on the employed sampling strategies and time-series analysis techniques to define network constituents. This, together with limitations in knowledge about the system's actual structural organization, calls for approaches to identify potentially superfluous network constituents. Here, we present such an approach. It is based on minuscule and elementary perturbations targeting single network constituents. Constituents are deemed potentially superfluous if the perturbations lead to no or only negligible changes of network characteristics, covering the local to global scale. We test our approach on various paradigmatic network models.**

## I. INTRODUCTION

Complex network approaches have been repeatedly shown to provide deeper insights into the structure and dynamics of spatially extended complex systems in diverse areas of science. In many natural and man-made networked systems, access to the underlying coupling structure may be restricted or even impossible.[1–12] Nevertheless, in such cases can the system be described by an interaction network with vertices representing subsystems or elementary units and edges representing interactions between them. This ansatz has been successfully applied, e.g., in the study of (functional) brain networks,[3,10] climate networks,[13,14] protein–protein interactions,[15] gene interactions,[16] plant–pollinator interactions,[17–19] food-webs,[20] or communication and social networks.[21,22]

When it comes to analyzing real-world complex systems, lacking explicit knowledge of the structural organization of the dynamical system under study is quite common. Hence, vertices of the related interaction network are commonly associated with sensors that are placed to sufficiently capture a subsystems' dynamics. Deriving edges from the system's dynamics is usually based on a data-driven quantification of interaction properties, namely, strength, direction, and coupling function. Given that interactions can manifest themselves in various aspects of the dynamics (amplitudes, frequencies, phases, etc.), a large number of time series analysis techniques are now available. The reliability of techniques, however, may be influenced by the mostly unavoidable finiteness of noisy field data, which can lead to erroneous estimates of interaction properties. Together with the fact that there is by now no commonly accepted method to derive binary or weighted (or weighted and directed) networks from interaction properties, this represents a source for severe misinterpretations of network properties.[23–30]

Yet, these issues are influenced and preceded by a more general problem: choosing the right number of sensors and placing them in a meaningful way. Arrangement and placement of sensors is highly non-trivial and most often leads to a spatial over- or undersampling of a system. These issues translate to the presence of additional and potentially superfluous constituents or the absence of potentially relevant constituents and may cause severe misinterpretations of network properties.[23–32] When investigating real-world systems, aiming to gather as much information as possible is rather common practice but bears the risk of oversampling the system. Hence, there is a strong need for methods that allow us to identify redundant or superfluous vertices and edges. For edges, a vast plethora of methods have been proposed,[33–37] although their suitability continues to be matter of debate.[38–41] Interestingly, the issue of identifying superfluous vertices has so far been addressed only rarely.[42,43]

We here propose a perturbation-based approach to identify potentially superfluous network constituents (vertices and edges), employing elemental and minuscule perturbations that directly target single constituents. With the premise that targeting constituents of a potentially superfluous nature has little to no effect on the characteristics of networks, exactly these are compared prior to and after perturbation. We test the suitability of this method on weighted small-world, scale-free, random, and complete networks.

## II. METHODS

There are several ways to perturb a network, with different types of perturbation potentially leading to different outcomes. Almost all perturbations, however, can be viewed as an accumulation, superposition, or interplay of the following, straightforward, and elementary perturbations:

1. vertex/edge removal: one or more constituents are removed from the network. In the case of removing a vertex, its connected edges are removed along with it. The removal of constituents can have a significant impact on the network's connectedness, and it can lead to the fragmentation of the network into smaller disconnected components;
2. vertex/edge addition: constituents are added to the network. This can increase the network's connectedness and can facilitate the exchange of information or resources in different ways;
3. rewiring: an edge is randomly rewired, possibly leading to changes in the network's topology. Rewiring can alter the network's characteristics, especially path-structural aspects;
4. weight changes: the weight of an edge is altered, possibly influencing local up to global network characteristics.

However, the influences of structurally minuscule perturbations are hard to determine and even harder to control on the level of the complex system. Previous research has shown that random perturbations can have a major influence on very specific macroscopic network characteristics.[44–46] Nonetheless, and especially when it comes to the investigation of real-world systems, it remains unclear, how on a general basis minuscule perturbations targeting single constituents change the respective networks. Thus far, comparing networks is a notoriously difficult task, particularly for networks of different sizes (and changes in network sizes often go hand in hand with these perturbations), and there is no commonly accepted and sufficient way to do so.[47,48] Hence, we can only focus on network metrics[49] that, in total, describe the network somewhat comprehensively (cf. Sec. II B and Table I).

The principal idea behind our perturbation-based approach now is that if the targeted perturbation of a network constituent (cf. Sec. II C) does not alter network characteristics assessed with the various metrics, or only to a small negligible extent, the targeted constituent can be deemed potentially superfluous.

### A. Employed perturbations

Of the above listed four elementary perturbations, only the first two are universally applicable in any kind of network, independent of its topology and definitions of edges (regarding weight, direction, or multiple edges). Based on these, we further differentiate between the following three perturbations that we will employ in the wake of our perturbation-based method to identify potentially superfluous constituents:

- vertex removal: a vertex $v$ and its connected edges $\{v, j\}$ are discarded, with $j$ denoting vertices adjacent to $v$;
- vertex cloning: a vertex $v$—that is already present in the network—is duplicated, including its connected edges $\{v, j\}$ by adding a vertex $v'$ and adding the respective edges $\{v', j\}$, with $j$ denoting vertices adjacent to $v$; cloned vertex $v$ and clone $v'$ are not directly connected;
- edge removal: an edge is discarded from the network.

Perturbations directly targeting a single vertex, hence, may indirectly affect edges connected to the respective vertex in the course of the perturbation.

### B. Network metrics

We generally differentiate between global and local network characteristics that are evaluated by network metrics (cf. Table I). Global network metrics describe the network as a whole, often associating a network characteristic with a single quantity. Local network metrics focus on aspects of single network constituents (vertices and edges) or groups of such. While some of these local metrics might still depend on the composition of the network as a whole, others merely depend on the direct neighborhood of the respective constituent.

A network consists of a set of vertices $\mathcal{V}$ ($v_i \in \mathcal{V}, i = 1, \ldots, V$; $V = |\mathcal{V}|$) and a set of edges ($e_n \in \mathcal{E}, n = 1, \ldots, E$; $E = |\mathcal{E}|$) with an edge connecting two vertices [$e_{ij} = (v_i, v_j)$]. The network can be described by its adjacency matrix $\mathcal{A} \in \{0, 1\}^{V \times V}$, with $\mathcal{A}_{ij} = 1$ if edge $e_{ij}$ exists between vertices $i$ and $j$, and $\mathcal{A}_{ij} = 0$ otherwise. Complementarily, for weighted networks, we define the weight matrix $\mathcal{W} \in [0, 1]^{V \times V}$, with $\mathcal{W}_{ij}$ referring to the edge weight (strength of interaction) between vertices $i$ and $j$.

#### *1. Global network metrics*

Some metrics of networks describe certain aspects of the network as a whole. This not only can allow the classification of network topologies but also allows the comparison of other characteristics of networks, such as network size, path-structure, degree-correlations, robustness, and stability.

**TABLE I.** Overview of global and local network characteristics and their respective quantifying metrics.

| | | Characteristics | Metrics |
|---|---|---|---|
| Global | network | Length of the longest shortest path between any pair of vertices in a network | (Pseudo) diameter $D$ |
| | | Average length of a path between any two vertices in a network | Average shortest path length $L$ |
| | | Extent to which vertices in the network tend to cluster together | Global clustering coefficient $G$ |
| | | Extent to which vertices with (dis-)similar properties are preferentially connected among themselves | Assortativity $A$ |
| | | Stability of the network's globally synchronized state | Synchronizability $S$ |
| Local | Vertices | Integration of a vertex in its direct neighborhood (binary network) | Degree $d$ |
| | | Integration of a vertex in its direct neighborhood (weighted network) | Strength centrality $\mathcal{C}_{\mathrm{v}}^{\mathrm{S}}$ |
| | | Extent to which a strongly integrated vertex is connected to other strongly integrated vertices | Eigenvector centrality $\mathcal{C}_{\mathrm{v}}^{\mathrm{E}}$ |
| | | Extent to which a vertex can reach any other vertex in the network via shortest paths | Closeness centrality $\mathcal{C}_{\mathrm{v}}^{\mathrm{C}}$ |
| | | Extent to which a vertex connects otherwise distant regions in the network | Betweenness centrality $\mathcal{C}_{\mathrm{v}}^{\mathrm{B}}$ |
| | Edges | Integration of an edge in its direct neighborhood | Nearest-neighbor centrality $\mathcal{C}_{\mathrm{e}}^{\mathrm{N}}$ |
| | | Extent to which a strongly integrated edge is connected to other strongly integrated edges | Eigenvector centrality $\mathcal{C}_{\mathrm{e}}^{\mathrm{E}}$ |
| | | Extent to which an edge can reach any other edge in the network via shortest paths | Closeness centrality $\mathcal{C}_{\mathrm{e}}^{\mathrm{C}}$ |
| | | Extent to which an edge connects otherwise distant regions in the network | Betweenness centrality $\mathcal{C}_{\mathrm{e}}^{\mathrm{B}}$ |

The **(pseudo) diameter** $D$ is the length of the longest shortest path between any pair of vertices in a network. The length of a path is chosen as the sum of the inverse of all edge weights on that path.

The **average shortest path length** $L$ quantifies the average length of a path $\psi$ between any two vertices ($\{z,l\} \in \mathcal{V}$) in a network,

$$L = \frac{\sum_{zl} \psi_{zl}}{V(V-1)}.$$

The **global clustering coefficient** $G$ quantifies to what extent network vertices tend to cluster together. For a weighted network, the global clustering coefficient is defined as

$$G = \frac{\mathrm{Tr}\mathscr{W}}{\sum_{z\neq l} [\mathscr{W}^2]_{zl}}.$$

**Assortativity** $A$ characterizes how vertices with (dis-)similar properties (here: strength, being the sum of the weights of the attached edges) are preferentially connected among themselves.[50,51] To calculate $A$, we estimate the (Pearson) correlation coefficient between the strengths of connected vertices,

$$A = \sum_{xy} xy(q_{xy} - a_x b_y)/\sigma_a \sigma_b,$$

with $x$ and $y$ representing strength values and $q_{xy}$ representing the fraction of edges that connect a vertex with strength $x$ to a vertex of strength $y$. Then, $q_{xy}$ satisfies the sum rules: $\sum_{xy} q_{xy} = 1$, $\sum_y q_{xy} = a_x$, $\sum_x q_{xy} = b_y$. $\sigma_a$ and $\sigma_b$ are the standard deviations of the distributions $a_x$ and $b_y$.

**Synchronizability** $S$ of a network describes the stability of its globally synchronized state.[52,53] We here characterize it by the eigenratio $S = \lambda_V/\lambda_2$. $\lambda_V$ denotes the largest eigenvalue and $\lambda_2$ the smallest non-vanishing eigenvalue of the network's Laplacian matrix $L_{zl} = s_z \delta_{zl} - \mathscr{W}_{zl}$ ($\delta$ is the Kronecker delta, $s_z$ denotes the strength of vertex $z$; see below).

### 2. Local network metrics

The concept of centrality has been introduced in many different fields and contexts.[54–70] The general idea is to quantify a constituent's role or importance in the larger network based on certain characteristics, primarily focusing on the integration of a constituent in the network due to specific aspects. Hence, centrality metrics can be utilized to measure importance yielding an importance ranking.[45,71,72]

The **degree** of a vertex $z$ is the sum of edges connected to this vertex: $d_z = \sum_{l=0}^{V} \mathscr{A}_{zl}$. Analogously, the **strength** (or **strength centrality**) of a vertex is the sum of edge weights of all edges connected to this vertex: $s_z = \mathcal{C}_{\mathrm{v}}^{\mathrm{S}}(z) = \sum_{l=0}^{V} \mathscr{W}_{zl}$.

Similarly, and in dependence of the edges adjacent constituents, with **nearest-neighbor centrality**,[70] an edge is considered to be more central the larger its weight and the more similar and the higher the strengths of the vertices which are connected by that edge. Nearest-neighbor edge centrality of an edge $z$ between vertices $a$ and $b$ is defined as[70]

$$\mathcal{C}_{\mathrm{e}}^{\mathrm{N}}(z) = \frac{\mathcal{C}_{\mathrm{v}}^{\mathrm{S}}(a) + \mathcal{C}_{\mathrm{v}}^{\mathrm{S}}(b) - 2w_z}{|\mathcal{C}_{\mathrm{v}}^{\mathrm{S}}(a) - \mathcal{C}_{\mathrm{v}}^{\mathrm{S}}(b)| + 1} w_z,$$

where $w_z = \mathscr{W}_{ab}$ denotes the edge weight and $z \in \{1, \dots, E\}$ and $(a, b) \in \{1, \dots, V\}$. Hence, nearest-neighbor centrality can be considered as a strength-based edge centrality concept. Much like the strength of a vertex, the nearest-neighbor centrality value of an edge is only influenced by its adjacent constituents.

**Eigenvector centrality** considers the influence of a vertex/edge (v/e) on the network as a whole. A constituent is regarded as central if adjacent constituents are also central. This centrality is defined as[68,73]

$$\mathcal{C}^{\mathrm{E}}_{\mathrm{v,e}}(z) = \frac{1}{\lambda_{\mathrm{max}}} \sum_{l} M_{zl}\, \mathcal{C}^{\mathrm{E}}_{\mathrm{v,e}}(l).$$

Here, $\lambda_{\mathrm{max}}$ denotes the dominant eigenvalue of matrix $\mathbf{M}$. In the case of vertices, $\left\{z, l\right\} \in \mathscr{V}$ and $\mathbf{M}$ denotes the weight matrix $\mathscr{W}^{(\mathrm{v})} \in [0,1]^{V\times V}$, with $\mathscr{W}^{(\mathrm{v})}_{zl}$ denoting the weight of an edge between vertices $z$ and $l$. We define $\mathscr{W}^{(\mathrm{v})}_{zz} := 0\,\forall\, z$ with $z \in \{1, \ldots, V\}$. In case of edges, $\left\{z, l\right\} \in \mathscr{E}$ and $\mathbf{M}$ denotes the weight matrix $\mathscr{W}^{(\mathrm{e})} \in [0,1]^{E\times E}$ whose entries $\mathscr{W}^{(\mathrm{e})}_{zl}$ are assigned the average weight of edges $z$ and $l$ if these edges are connected to a same vertex, and 0 otherwise. As above, we define $\mathscr{W}^{(\mathrm{e})}_{zz} := 0\,\forall\, z$ with $z \in \{1, \ldots, E\}$. The aforementioned definition is applied iteratively until eigenvector centrality values remain stable. Eigenvector centrality can be considered as a strength-based centrality concept, which, due to its recursive definition, relates a constituent to all the other constituents in the network.

**Closeness centrality** considers the distance between a constituent and all other constituents in a network. A constituent with a high closeness centrality is central as information from this constituent can reach all other constituents in the network via short paths, and so the constituent can exert a more direct influence over the network. The closeness centrality of vertex $z$ is defined as[74]

$$\mathcal{C}^{\mathrm{C}}_{\mathrm{v}}(z) = \frac{V-1}{\sum_l d_{zl}},$$

with $(z, l) \in \{1, \ldots, V\}$ and where $d_{zl}$ is the length of the shortest path between vertices $z$ and $l$, calculated as the sum of the inverse of all edge weights on the path. The closeness centrality of edge $z$ between vertices $a$ and $b$ can be defined as[68]

$$\mathcal{C}^{\mathrm{C}}_{\mathrm{e}}(z) = \frac{E-1}{\sum_l (d_{la} + d_{lb})} = \frac{E-1}{\frac{1}{\mathcal{C}^{\mathrm{C}}_{\mathrm{v}}(a)} + \frac{1}{\mathcal{C}^{\mathrm{C}}_{\mathrm{v}}(b)}}$$
$$= (E-1)\frac{\mathcal{C}^{\mathrm{C}}_{\mathrm{v}}(a)\mathcal{C}^{\mathrm{C}}_{\mathrm{v}}(b)}{\mathcal{C}^{\mathrm{C}}_{\mathrm{v}}(a) + \mathcal{C}^{\mathrm{C}}_{\mathrm{v}}(b)},$$

with $z \in \{1, \ldots, E\}$ and $(a, b, l) \in \{1, \ldots, V\}$. Hence, closeness centrality can be considered as a path-based centrality concept, which is, therefore, influenced by the network as whole.

**Betweenness centrality** is a measure of how frequently a shortest path traverses a given constituent. A constituent with a high betweenness centrality value is central because it acts as a bridge between other parts of the network. Vertex/edge betweenness centrality (of vertex/edge $z$) can be defined as[56,68,75,76]

$$\mathcal{C}^{\mathrm{B}}_{\mathrm{v,e}}(z) = \frac{2}{F} \sum_{l \neq m} \frac{q_{lm}(z)}{G_{lm}},$$

where $z \in \{1, \ldots, V\}$ (for vertices), respectively, $z \in \{1, \ldots, E\}$ (for edges), $\left\{l, m\right\} \in \{1, \ldots, V\}$, $q_{lm}(z)$ is the number of shortest paths between vertices $l$ and $m$ running through vertex/edge $z$, and $G_{lm}$ is the total number of shortest paths between vertices $l$ and $m$. Again, the length of a path is chosen as the sum of the inverse of all edge weights on that path. The normalization factor is $F = (V-1)(V-2)$ in the case of vertices and $F = V(V-1)$ in the case of edges. Betweenness centrality can be considered as a path-based centrality concept, which is, therefore, influenced by the network as whole.

In order to be able to compare results yielded by different centrality concepts qualitatively, we introduce a centrality-value-based ranking of the networks constituents. A vertex/edge is assigned rank 1 if the largest centrality value is associated with it. The rank increases in increments of 1 for the vertex/edge with second largest centrality value, third largest centrality value, etc., yielding an increasing rank as centrality values decrease. We abstain from assigning two or more constituents the same rank and rank in order of appearance for equal centrality values.

## C. Perturbations of network constituents

For a given realization of a network (out of $N_{\mathrm{r}}$ realizations),

- we estimate local and global network metrics (cf. Sec. II B) and deduce an initial ranking of the network's constituents based on their centrality values. The latter allows us to identify a constituent, based on its rank, in the different realizations;
- we iterate over all network constituents and
  - employ the respective perturbation (cf. Sec. II A) to the test if the respective constituent $\gamma$ is potentially superfluous,
  - estimate local and global network metrics for this perturbed network, and
  - quantify the influence of the perturbation by comparing local and global network metrics prior and after the perturbation (cf. Sec. II D).

## D. Quantifying influences of network perturbations

In the case of the global network characteristics, we track the perturbed constituent $\gamma$ throughout the realizations of a given network via its respective rank $r_{\mathrm{u}}(\gamma)$ prior to perturbation (estimated with $\mathcal{C}^{\mathrm{S}}_{\mathrm{v}}$ for vertices and with $\mathcal{C}^{\mathrm{N}}_{\mathrm{e}}$ for edges). Generally, we expect the structurally minuscule perturbations to also have a negligible impact on any global network characteristics, if such does not strongly depend on the number of vertices or the number of edges. We calculate the average percentage change (from $N_{\mathrm{r}}$ realizations) of each metric resulting from the perturbation as

$$\overline{\delta\mu^{(r_{\mathrm{u}}(\gamma))}} = \frac{1}{N_{\mathrm{r}}} \sum_{i=1}^{N_{\mathrm{r}}} 100\, \frac{\mu_{i,\mathrm{u}} - \mu^{(r_{\mathrm{u}}(\gamma))}_{i,\mathrm{p}}}{\mu_{i,\mathrm{u}}}.$$

Here, $\mu \in \{D, L, G, A, S\}$, $\mu_{i,\mathrm{u}/p}$ denotes the global metric of the unperturbed/perturbed network (of realization $i$) and $r_{\mathrm{u}}(\gamma) \in \{1, \ldots, V\}$ (for vertices), respectively, $r_{\mathrm{u}}(\gamma) \in \{1, \ldots, E\}$ (for edges) is the rank of the perturbed constituent ($\gamma$) in the unperturbed network.

In the case of the local network characteristics and when investigating a change in centrality values, it is important to recognize that there is no one true centrality concept. Each of the centrality concepts employed here does focus on different topological aspects of the network. However, we can generally divide the centrality concepts into strength-based (nearest-neighbor centrality and eigenvector centrality) and path-based (betweenness centrality and closeness centrality) concepts. Hence, it is not necessarily

**TABLE II.** Percentage increase/decrease (as well as standard deviation and maximum value) of global network characteristics under respective perturbation and averaged over all constituents and all investigated networks ($\langle\bullet\rangle$). *D* diameter; *L* average shortest path length; *G* global clustering coefficient; *A* assortativity; *S* synchronizability.

| | Metrics | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Perturbation | $\langle\overline{\delta D}\rangle$ | $\sigma(\overline{\delta D})$ | $\max(\lvert\delta D\rvert)$ | $\langle\overline{\delta L}\rangle$ | $\sigma(\overline{\delta L})$ | $\max(\lvert\delta L\rvert)$ | $\langle\overline{\delta G}\rangle$ | $\sigma(\overline{\delta G})$ | $\max(\lvert\delta G\rvert)$ | $\langle\overline{\delta A}\rangle$ | $\sigma(\overline{\delta A})$ | $\max(\lvert\delta A\rvert)$ | $\langle\overline{\delta S}\rangle$ | $\sigma(\overline{\delta S})$ | $\max(\lvert\delta S\rvert)$ |
| Vertex removal | −1.5 | 4.85 | 16.66 | −0.81 | 1.47 | 29.33 | −0.19 | 2.01 | 15.93 | −1.01 | 12.44 | 39.63 | −4.87 | 19.83 | 1047.42 |
| Vertex cloning | −0.01 | 0.06 | 1.76 | 0.03 | 0.24 | 5.69 | 0.91 | 1.55 | 9.73 | −0.37 | 13.74 | 53.97 | −1.62 | 3.23 | 21.8 |
| Edge removal | −0.56 | 2.02 | 9.46 | −0.42 | 0.71 | 28.37 | 0.37 | 1.19 | 6.65 | −0.39 | 4.6 | 24.98 | −1.72 | 8.73 | 1047.74 |

to be expected to observe perturbation-induced changes in the distribution of strength-based centrality values, when observing a perturbation-induced change in the distribution of path-based centrality values (or vice versa). Nevertheless, in order for a targeted constituent to be considered potentially superfluous, the respective perturbation should not lead to meaningful changes in either distribution. For the employed perturbations, we would expect largely comparable distributions of centrality values for a given network prior to and after perturbation (independent of the centrality concept). The values of a given centrality metric, for a given network prior to and after perturbation, can, therefore, be considered to be drawn from the same distribution, and we test this null hypothesis using the Kolmogorov–Smirnov test. The null hypothesis is rejected for $p < 0.05$. Hence, if the null hypothesis can be rejected for a certain perturbation, and with regard to any of the centrality concepts, the perturbed network constituent cannot be considered potentially superfluous under this perturbation. However opposite reasoning, deeming a constituent as potentially superfluous is not valid if the respective perturbation did not lead to significant changes between the distributions of centrality values of the unperturbed and perturbed network. Still, it can be a further indication of the targeted constituent being potentially superfluous. Nonetheless, the specific local changes in the importance ranking of constituents can be abundant and meaningful in a greater context, while the distribution of centrality values is left unaltered.

In the case of the importance hierarchies, as deduced from the centrality-based rankings of a networks' constituents (vertices and edges, respectively), we quantify the local impact of a perturbation of constituent $\gamma$ by considering the following metric, calculating the difference $\Delta^{\bullet}_{\mathrm{v/e}}$ between the ranks[77] $r_{\mathrm{u}}(z)$ and $r_{\mathrm{p}}(z)$ of any constituent $z \neq \gamma$ ($z \in \mathscr{V}$ for vertices (v) and $z \in \mathscr{E}$ for edges (e)) for the unperturbed and the perturbed network:

$$\Delta^{\bullet}_{\mathrm{v/e}}(z) = |r_{\mathrm{u}}(z) - r_{\mathrm{p}}(z)|,$$

where $\bullet \in \{\mathrm{S,E,C,B}\}$ denotes the centrality concept employed for the ranking. $\Delta^{\bullet}_{\mathrm{v/e}}(z) \to 0$ can be considered as a further indication for constituent $\gamma$ to be potentially superfluous. The median value of $\Delta^{\bullet}_{\mathrm{v/e}}(z)$ is expected to be rather small.

Overall, deeming a network constituent potentially superfluous cannot be considered an absolute truth but is rather an assessment of a number of indications based on observed changes in network characteristics due to specific perturbations. The more qualifying observations can be made regarding these network characteristics—for the respective perturbation—the more considerable is a potential superfluous nature of the targeted constituent.

We, thus, set three criteria that indicate a constituent targeted by the respective perturbations to be considered potentially superfluous: negligible changes in a number of global network metrics, negligible changes in the distributions of centrality values (based on multiple centrality concepts), and negligible changes in the actual importance hierarchies of the constituents.

With regard to potentially dependencies of the aforementioned criteria, such as network topology, size and edge density, and, thus, with an eye on potential applications in the analyses of real-world systems, we investigate the suitability of these criteria analyzing various networks with preset properties.

## III. NETWORKS INVESTIGATED

When approximating real-world complex systems with networks, the latter are often associated with specific topologies (or combinations of such). Independent of the underlying complex systems, these topologies can have quite distinct properties that may not only influence network characteristics substantially but also can induce superfluous constituents, at least in some of their realizations. As an example, it may naively be expected to find superfluous information in a very dense and large network (e.g., large random networks) while it is rather less likely to find such in sparse networks (e.g., small-world or scale-free networks) or in networks with regular structures (e.g., lattices or rings).

We here consider undirected, weighted, and connected networks without self-loops or multiple edges. In the following, edge weights are drawn from a uniform distribution $U(0,1)$. We investigate four different topologies and networks of different sizes ($V \in \{20, 50, 100, 200, 500, 1000\}$) and different edge densities. Each network type of the following four topologies will be realized $N_{\mathrm{r}} = 100$ times:

- small-world networks[78] with rewiring probabilities $p \in \{0.01, 0.1, 0.2, 0.3\}$ starting from a ring with $m \in \{4, 8\}$ nearest-neighbors being connected,
- random networks[79,80] with edge creation probabilities $q \in \{0.05, 0.1, 0.2, 0.3, 0.5, 0.7\}$,
- scale-free networks[81] with the newly added vertices preferentially attached to existing vertices of high degree with $k \in \{4, 6, 10\}$ edges, and
- complete networks.

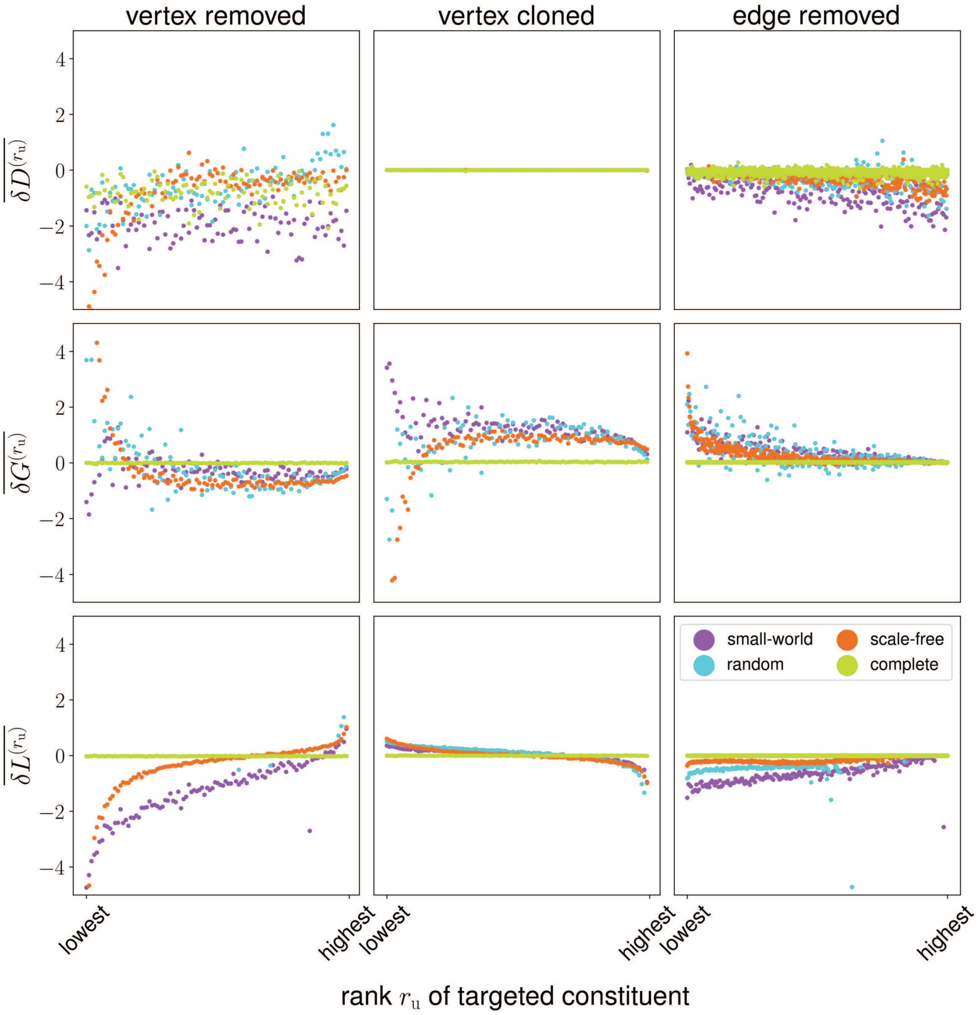

**FIG. 1.** Averages of percentage changes of (pseudo) diameter $\overline{\delta D^{(r_u)}}$, of global clustering coefficient $\overline{\delta G^{(r_u)}}$, and of average shortest path length $\overline{\delta L^{(r_u)}}$ under the respective perturbation of a targeted constituent with a certain rank $r_u$. Vertex ranks estimated with strength centrality and edge ranks estimated with nearest-neighbor centrality prior to perturbation. Averages from 100 realizations of each of four exemplary network types (small-world network: $V = 100$, $m = 4$, $p = 0.2$—random network: $V = 100$, $q = 0.05$—scale-free network: $V = 100$, $k = 4$—complete network: $V = 100$).

The edge density for a network is then defined as

$$\varrho = E/E_{\max} = E/\binom{V}{2} = \frac{2E}{V(V-1)}.$$

## IV. RESULTS

### A. Impact of perturbations on global network characteristics

For each of the three types of perturbation and predominantly independent of the network topology, we observe—overall and on average—perturbation-induced changes of global network metrics in the order of a few percent (<5%, cf. Table II). It is to be mentioned that while, on average, pointing to rather negligible changes, we do observe large maximum changes in a few, specific networks—primarily observed for assortativity (up to ∼50%) and synchronizability (up to ∼1000%)—the latter pointing toward the existence of some rare but seemingly vital constituents regarding the stability of a synchronized state particularly in random and complete networks.

Furthermore, we do observe dependencies regarding the importance $r_u$ of the constituent targeted by the perturbation, for at least some of the global network metrics. Yet, these dependencies vary regarding the network topology. Especially for those network topologies that are less random and of more regular structure (small-world and scale-free networks) the magnitude of changes of global clustering coefficient and average shortest path length (but also of assortativity and synchronizability; data not shown) depend on the importance $r_u$ of the removed/cloned constituent. Generally, largest total changes of metrics can be observed when removing/cloning most and least important constituents (cf. Fig. 1).

Surprisingly, we also observe not the removal of an edge but the cloning of a vertex to have the smallest average impact on four of the five global network metrics, even though removing a single edge is arguably a smaller structural network perturbation. It can be concluded that the employed network perturbations overall lead to

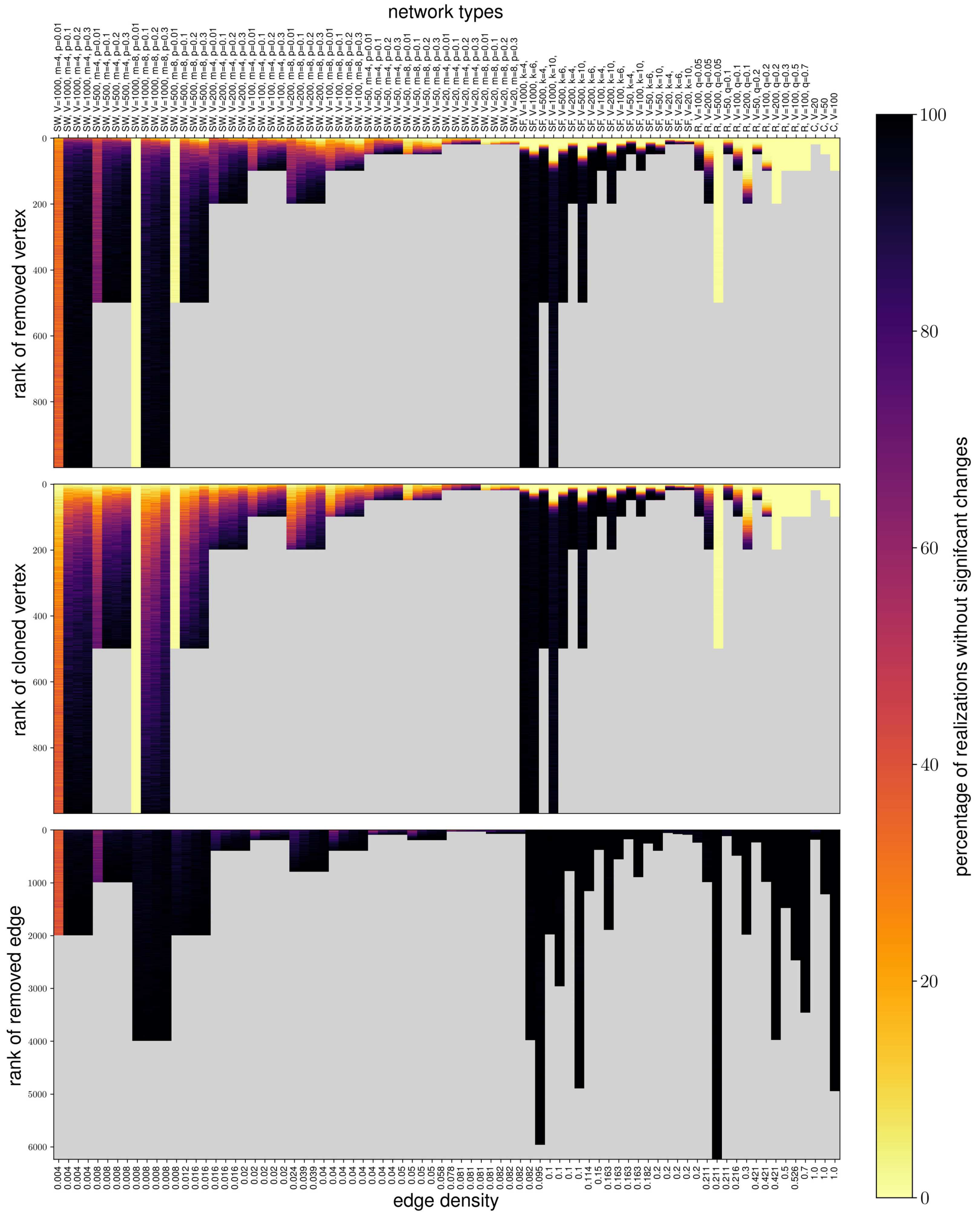

**FIG. 2.** Percentage of network realizations (color-coded) that show no significant change in either of the centrality distributions (cf. Sec. II D) when removing/cloning a constituent of a given rank $r_u$ (estimated with strength/nearest-neighbor centrality, in the respective network) (SW small-world network; SF scale-free network; R random network; C complete network). Empty cells—due to differences in network size—are colored in gray.

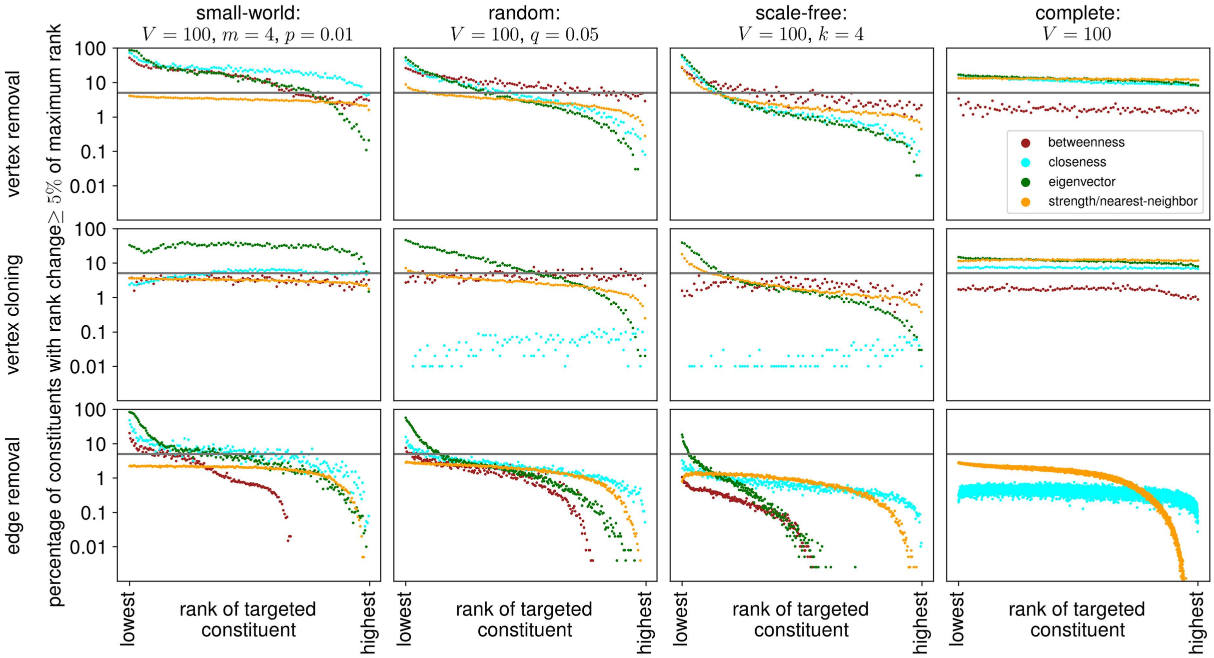

FIG. 3. Percentage of constituents with rank changes $\geq\theta$ of the maximum possible rank change in dependency of the rank of the constituent targeted by the respective perturbation (rows). We here chose $\theta \geq 5\%$ as this amounts to $\Delta^{\bullet}_{\mathrm{v/e}} \geq 1$ in the case of the smallest investigated networks with $V = 20$. Ranking is done via different centrality concepts (color-coded). Data are averaged over 100 realizations of each of four exemplary network types (columns): small-world network ($V = 100$, $m = 4$, $p = 0.2$), random network ($V = 100$, $q = 0.05$), scale-free network ($V = 100$, $k = 4$), and complete network ($V = 100$). The black horizontal line is for eye guidance only and represents 5% of possible constituents showing a rank change $\Delta^{\bullet}_{\mathrm{v/e}} \geq 1$. Similar relations are observed for $20 \geq V \geq 1000$.

minuscule changes in global network characteristics. Nevertheless, it is vital to realize that the observed changes can depend on the targeted constituents' importance. Our results indicate that particularly those constituents at neither end of the importance ranking can be deemed potentially superfluous.

## B. Impact of perturbations on local network characteristics

The observed dependencies of changes of global network characteristics regarding the targeted constituent's importance $r_{\mathrm{u}}$ and the type of perturbation indicate that similar changes and dependencies can be observed on smaller network scales as well. In the case of local network metrics, we first investigate whether deviations in the distribution of centrality values—for any of the four centrality concepts (vertex and edge centralities, respectively)—can be observed after perturbation (cf. Sec. II D). If centrality values from an unperturbed and perturbed network can generally be considered to be drawn from different distributions, the removed/cloned vertex/edge can hence not be deemed potentially superfluous. Naively viewed, it is still apparent that of the three perturbations, removing a single edge is the smallest structural network alteration, as removing/cloning a vertex would also include the removal/cloning of attached edges. Hence, it is generally to be expected that removing an edge has not only the smallest impact but potentially no impact

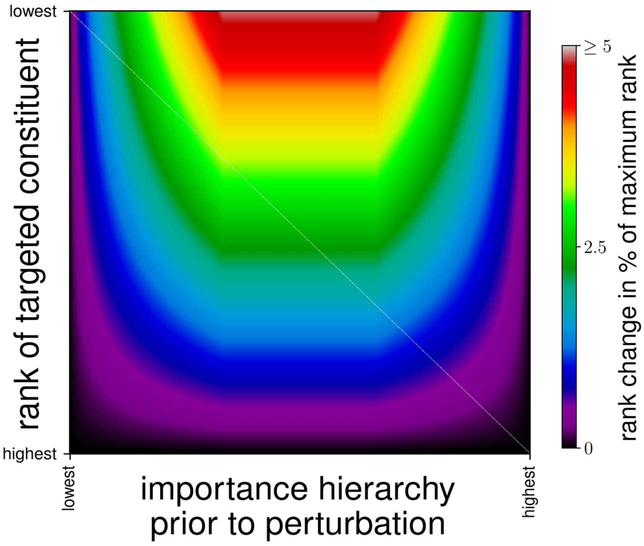

FIG. 4. Schematic depiction of changes in rank for each constituent (with importance hierarchy prior to perturbation) in dependency on the rank of the targeted constituent.

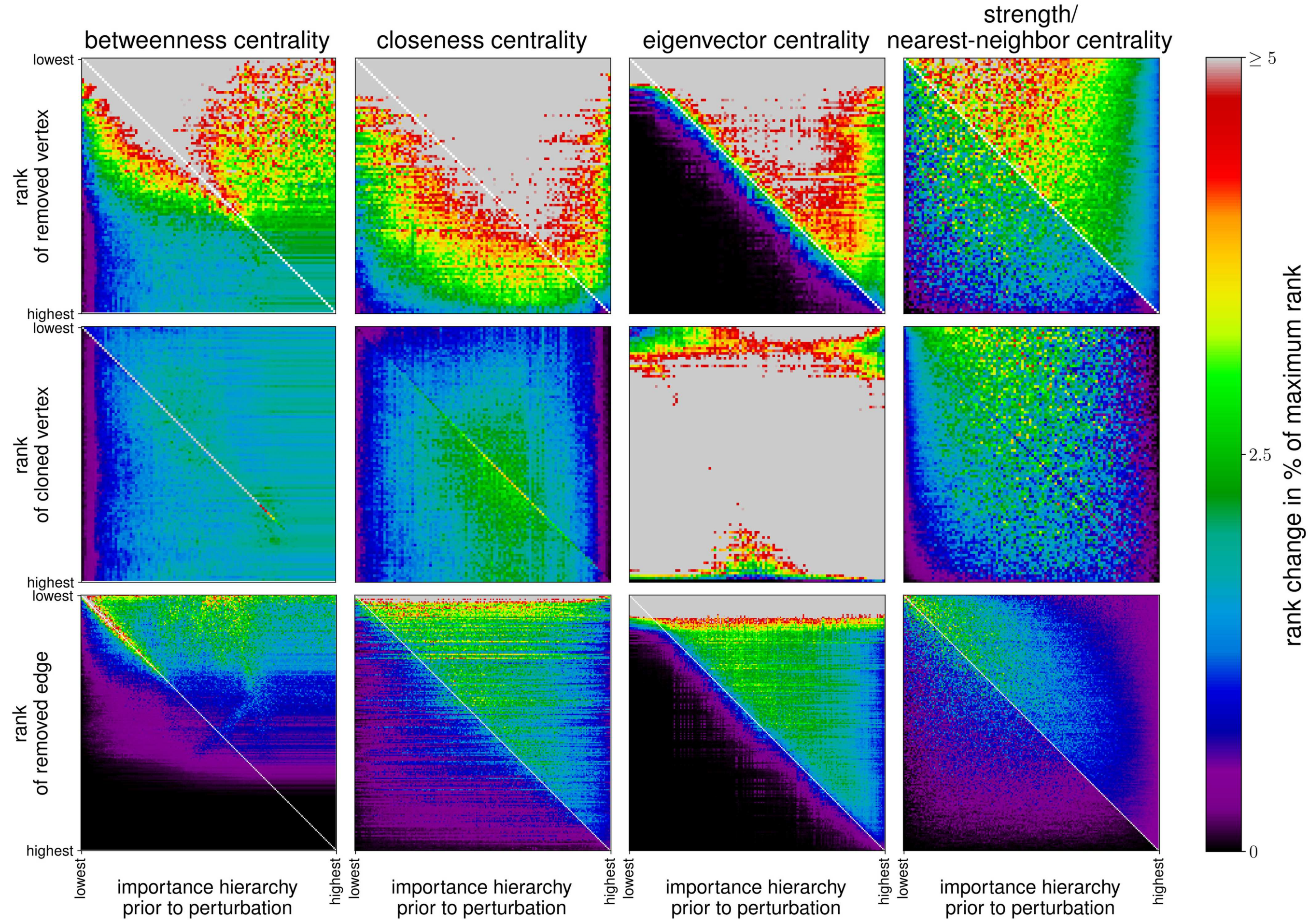

**FIG. 5.** Changes in rank for each constituent (with importance hierarchy prior to perturbation) in dependency on the rank of the targeted constituent in a small-world network with $V = 100$, $m = 4$, and $p = 0.01$.

at all on the distribution of centrality values compared to removing or cloning a vertex.

Figure 2 shows that the respective perturbations did not lead to a significant change in the distribution of centrality values in the majority of investigated networks. We do, however, observe the changes to strongly depend on network topology, type of perturbation, and rank $r_u$ of removed/cloned constituent. In the case of removing an edge, we only observe very few significant changes whatsoever in small-world networks with small rewiring probability ($p = 0.01$). Their almost regular structure explains why removing only important edges still can lead to changes in the distribution of centrality values in at least some of the realizations of networks ($<40\%$), as removing such an important edge from the network will lead to large changes in the path-structure and, thus, will greatly affect centrality values estimated with path-based centrality metrics. Similar effects, which can be explained in an analogous way, regarding these specific small-world networks (the 12 small-world network types with $p = 0.01$) are observed when removing or cloning a vertex. The more regular the network, the stronger is the alteration of the regular structure when introducing or removing a vertex and its respective edges. Furthermore, as the ranking in the case of the vertices is done via the strength centrality, it can be deduced that the more important the vertex, the larger is its integration in its direct neighborhood within the network (cf. Table I). Therefore, the more important the removed/cloned vertex, the larger the alteration of the network's structure.

In particular, the aforementioned small-world networks that are large in size and have a high edge density ($V \in \{500, 1000\}$, $m = 8$) show the largest amount of significant changes. This is, otherwise, only observed for networks with largest possible edge densities (fully connected networks) or comparably large random networks ($V = 500$). For these large and/or dense networks, cloning a vertex will consequently result in adding a large amount of edges, due to cloned vertex' high degree. Likewise, removing a vertex

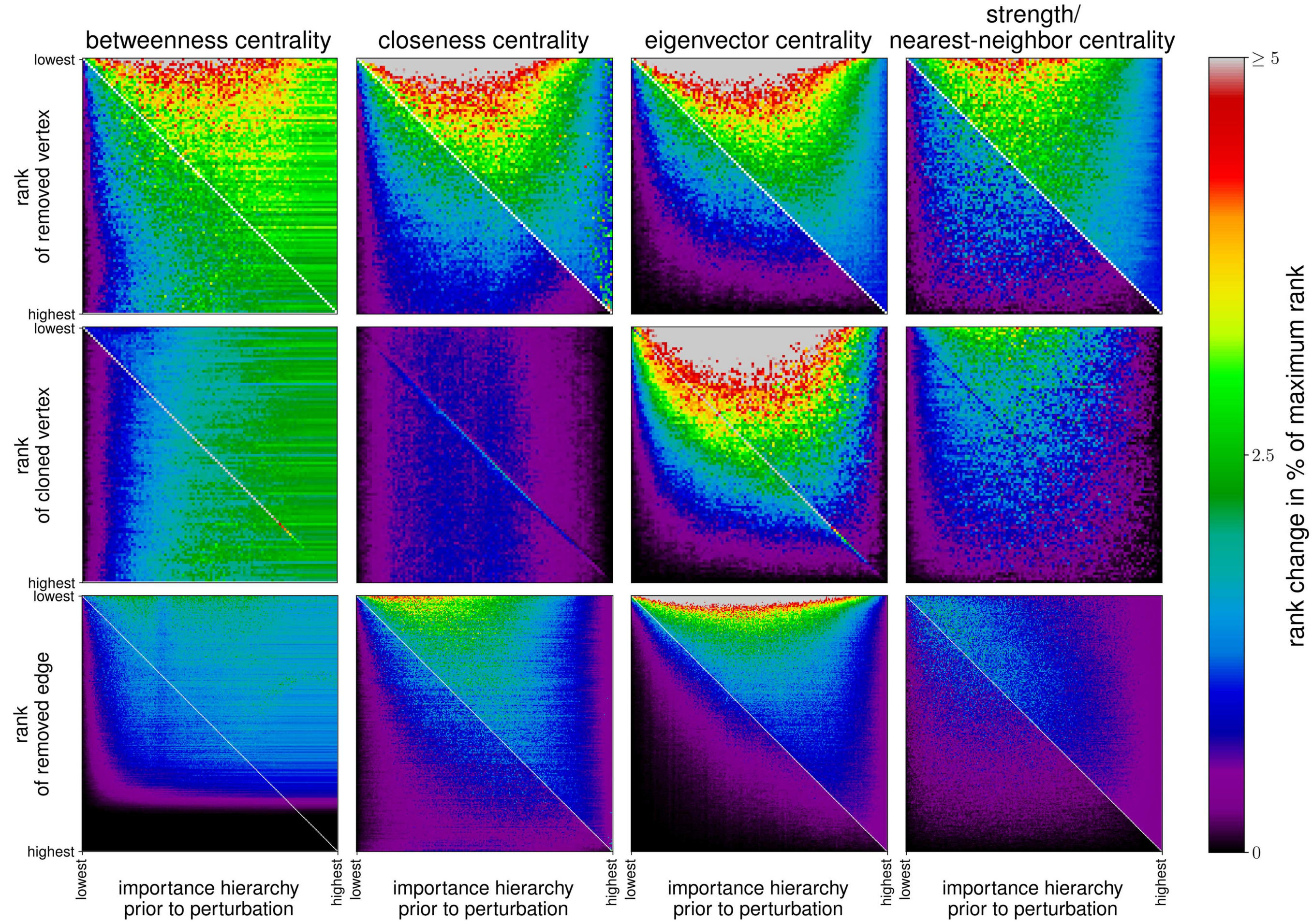

**FIG. 6.** Same as Fig. 5 but for a random network with $V = 100$ and $q = 0.05$.

includes removing a large amount of edges in these networks. Both perturbations, hence, result in large changes of the distributions of centrality values.

In the case of the less regular and less dense networks (random networks with $V < 500$, small-world networks with $0.01 < p < 1.0$, scale-free networks), the observed changes in centrality values highly depend on which vertex was removed/cloned. The amount of network realizations with significant changes in the distributions of centrality values (regarding the respective perturbation) decreases with increasing rank (decreasing importance) of the targeted vertex. This once again is likely explained by the high interconnectedness (high degree) of important vertices. Cloning the most important vertex always—in 100 % of the realizations—led to significant changes of the distribution of centrality values with regard to the unperturbed network. Furthermore, and especially in small-world networks, even cloning less important vertices much more often led to significant changes than removing said vertices.

We can conclude that the structurally smallest perturbation, namely, removing a single edge, has the overall smallest influence on the distribution of centrality values and that removing a vertex less often leads to significant changes than cloning said vertex. Furthermore, removing/cloning an important constituent has a stronger impact than removing a less important constituent. Almost regular as well as dense and large networks are most strongly affected by perturbations targeting vertices. Our results here, and in contrast to those reported on in Sec. IV A, indicate that particularly those constituents identified as less important prior to perturbation (high rank), may qualify as potentially superfluous.

### C. Impact of perturbations on importance hierarchy

Having observed mostly insignificant changes in the distribution of centrality values, at first glance, points toward a weak and minimal alteration of the network. Yet, the importance hierarchies of network constituents might have changed greatly. As a most extreme example: the constituents with respectively highest and smallest centrality value prior to perturbation exchange their

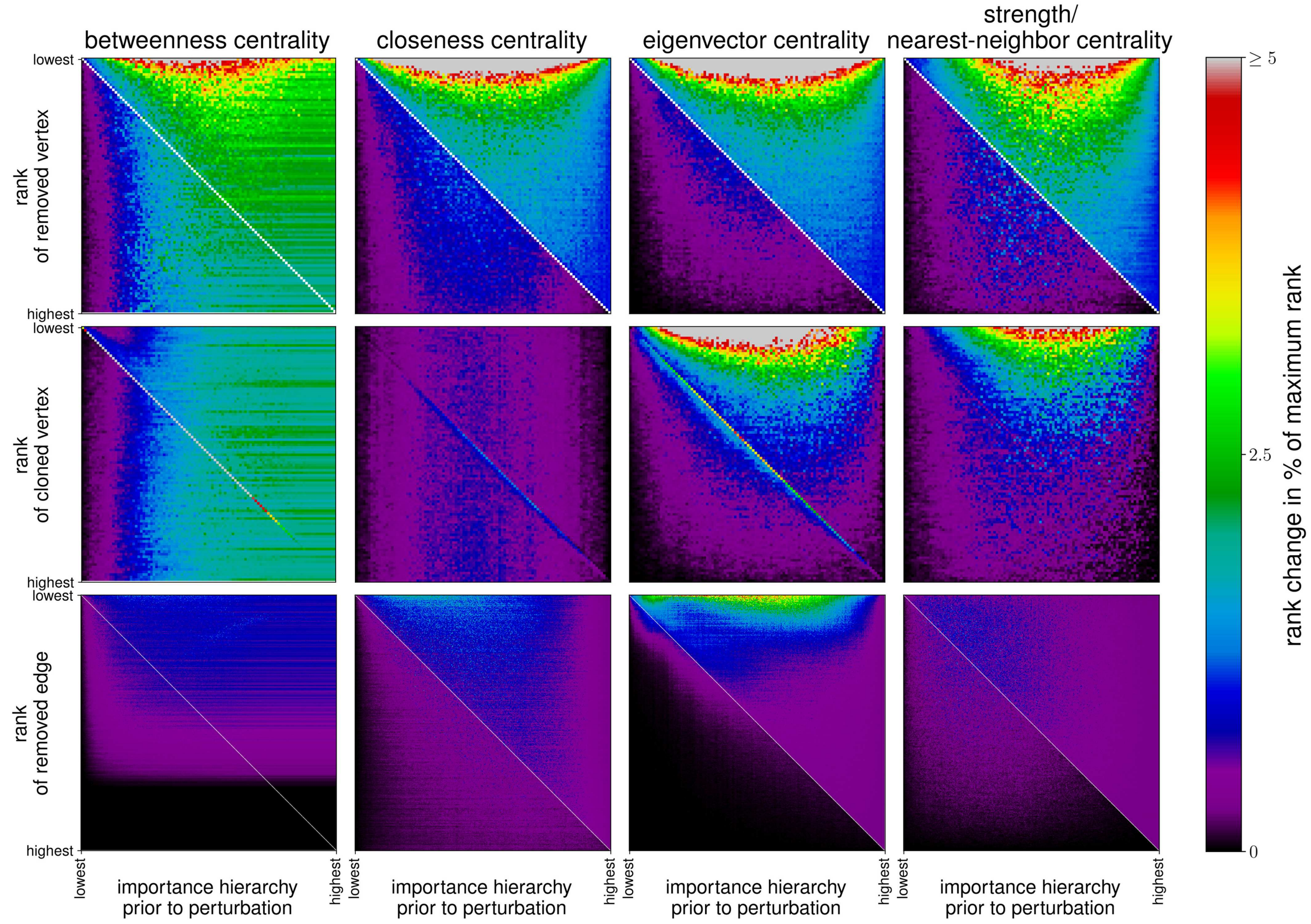

**FIG. 7.** Same as Fig. 5 but for a scale-free network with $V = 100$ and $k = 4$.

positions in the ranking as a result of the perturbation. A constituent with little importance prior to perturbation is now, after the employed perturbation, considered the most important constituent and vice versa, while the distribution of centrality values remained the same. Furthermore, changes in the importance hierarchies can be used to identify if constituents that are directly affected by the perturbation (e.g., removed or cloned) can be deemed potentially superfluous. To this end, we investigate the changes in constituents ranks due to the respective perturbations (cf. Sec. II D).

It can be deduced from Fig. 3 that, largely independent of the employed perturbation, the changes in the importance hierarchies depend on the constituent's rank $r_u$ targeted by the perturbation. Perturbing constituents with small rank (high importance) in comparison to those with high ranks (low importance) tends not only to lead to greater rank changes of single constituents but also to more constituents showing such changes ($\Delta^{\bullet}_{v/e} \gg 0$) overall. Widely independent of the networks' topologies, we observe that the smaller the rank $r_u$ (the higher the importance) of the perturbed constituent, the larger are the changes in the total ranking of the constituents. This general relationship can be observed with each of the employed centrality concepts, while the precise functional relationship depends on multiple factors such as network size, network topology, type of perturbation, and centrality concept.

The quantitative nature of these relationships regarding perturbation and centrality concept is exemplary depicted in the Appendix (cf. Figs. 5–8) for some network models, highlighting not only the overall stronger effect on the ranking when targeting important constituents but also the fact that the rankings of all the other constituents are affected very distinctly depending on their respective rank prior to perturbation (schematically depicted in Fig. 4). In particular, in the case of removing vertices, we observe that constituents at either end of the importance hierarchy are affected less by this perturbation than constituents with median rank. Our results here are in line with those reported in Sec. IV B and indicate that particularly those constituents identified as less important prior to perturbation can be deemed potentially superfluous.

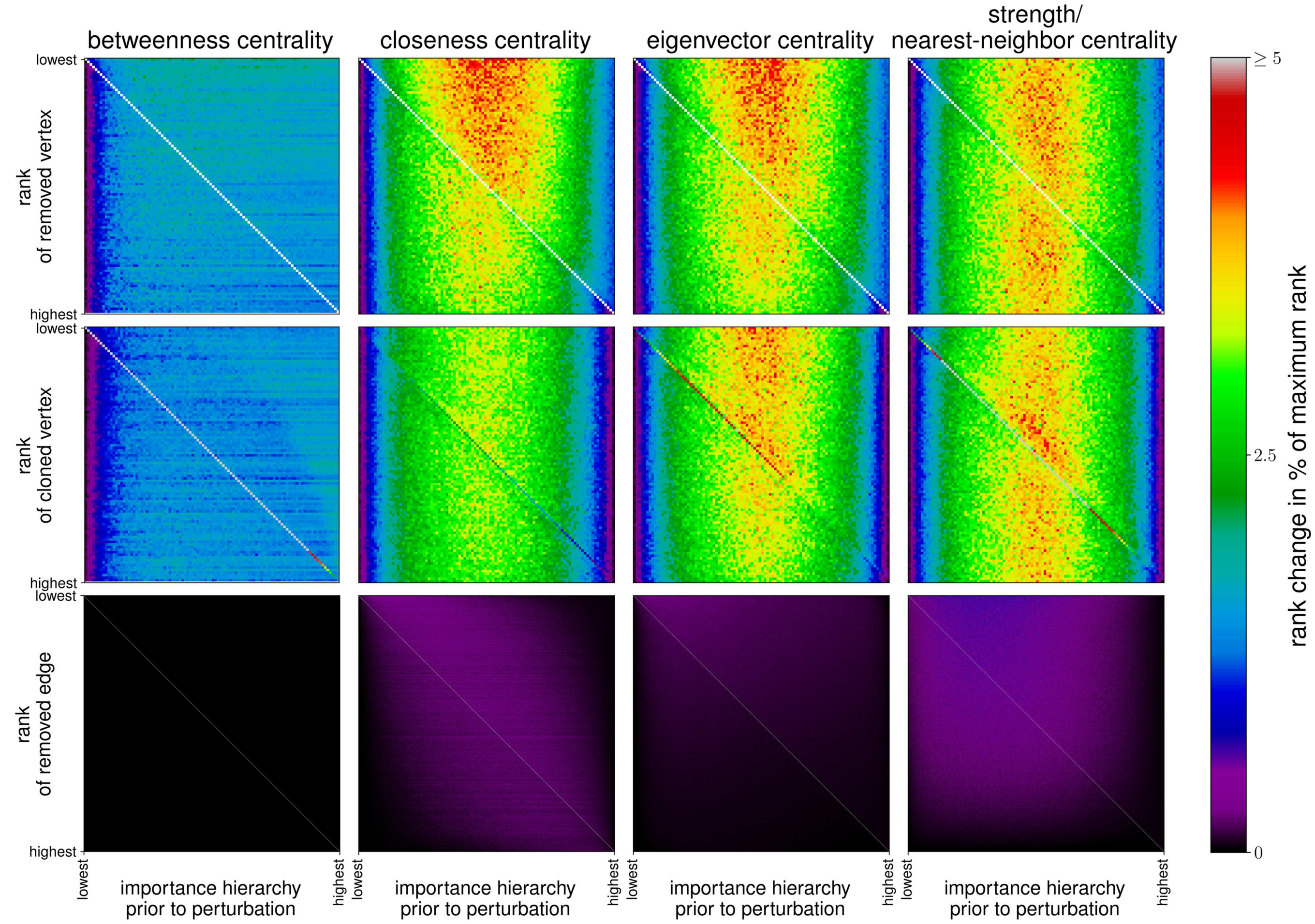

**FIG. 8.** Same as Fig. 5 but for a complete network with $V = 100$.

## D. Concluding remarks

It is to conclude that while aspects such as the path-structure, degree-correlations, robustness, and stability are, largely and on average, left unaltered by the employed perturbations, we do observe high dependency of changes of metrics $\overline{\delta\mu}$ regarding the rank of the constituent targeted by the perturbation. This points toward a possible intrinsic existence of potentially superfluous constituents in the networks investigated here. Observing changes in the rankings of constituents (as determined with different centrality concepts) consolidates these findings. In particular, targeting constituents with low rank (high importance) in comparison to targeting constituents with high rank (low importance) led to greater changes in these rankings and revealed dependencies regarding the network topology.[77] This shows that—arguably contrary to expectation—less dense networks and also less regular networks (following no trivial geometric arrangements such as a ring or a lattice) can contain more potentially superfluous constituents than, for example, very dense and even complete network. For the investigated networks, we can conclude that the three criteria point toward constituents of tendentially low (but not least) importance, to be potentially superfluous.

## V. DISCUSSION

We here proposed a perturbation-based method in order to tackle the extensive problem of identifying potentially superfluous network constituents. We formulated the premise that the instant absence or additional presence of a potentially superfluous network constituent should lead to negligible changes in network characteristics only, which do not trivially depend on even the smallest change in network size. Making use of minuscule and elemental perturbations, targeting single constituents directly, we investigated whether such perturbations lead to changes in global as well as local metrics that describe the investigated networks rather comprehensively. The less changes we observe for the metrics when perturbing the respective network constituent, the more this is an indication for this constituent to be of potentially superfluous nature. We formulated three criteria, which can provide important information when it comes to identifying potentially superfluous constituents.

It is generally to be expected that, independent of the investigated real-world system, certain network topologies may contain superfluous constituents, simply due to their structural makeup. Following this line of thinking, it is to be expected that the sheer size and density of complete networks should provide a great possibility for the existence of such potentially superfluous constituents. Likewise, it is easy to understand that certain regular structures, e.g., a ring or a lattice with a large amount of nearest- and next-nearest-neighbors connections, are more likely to contain potentially superfluous constituents than a ring/lattice with only nearest-neighbors connections.

We could confirm that—even though generally shown to have a small influence on local as well as global characteristics[49,82–84]—the here investigated effects of employed perturbations indeed largely differ for different network topologies as revealed with the three criteria. While we could show that size and edge density affect the values of global network metrics, the here employed minuscule perturbations, on average, led to negligible changes in these values. On the other hand, regular structures, whether it be a ring/lattice or a complete network, were especially prone to be influenced in their local characteristics.

Although in almost regular networks an importance hierarchy is dominated by edge weights, the said importance hierarchy in less regular networks might be influenced by their distinct topological makeup (small-world or scale-free networks). This makes it rather hard to get an intuitive feeling about the existence of potentially superfluous constituents in these complex network topologies. However, contrary to expectation, our perturbation-based approach points to far less potentially superfluous constituents in complete and regular networks than in more complex topologies such as small-world and scale-free networks.

Nevertheless, independent of the networks' topology, if the perturbation targeted a more important constituent, the changes in local network characteristics (distribution of centrality values and centrality-based rankings) were also larger, in comparison to targeting a less important constituent. This also shows that *a priori* knowledge about the importance hierarchy of the networks' constituents might not only be highly useful but in some cases even necessary to end up with a satisfactory and somewhat accurate representation of a real-world complex system. In addition, and especially in those cases for which a priori knowledge about the network's actual structure is either not accessible or very limited, our perturbation-based approach can aid in identifying potentially superfluous and likewise indispensable network constituents.

Future studies should focus on employing the presented approach to identify potentially superfluous constituents either in networks with built-in superfluous constituents or in networks constructed from empirical observations prone to have superfluous constituents. Further investigations considering scenarios from real-world issues (like noise contamination and other measurement errors[85]) might aid in a more accurate modeling of real complex (dynamical) systems. This could mean taking into account not necessarily the exact cloning of network constituents but a combination of cloning and perturbations regarding the edge weights of cloned edges.

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## AUTHOR DECLARATIONS

### Conflict of Interest

The authors have no conflicts to disclose.

### Author Contributions

**Timo Bröhl:** Conceptualization (equal); Data curation (equal); Formal analysis (equal); Funding acquisition (equal); Investigation (equal); Methodology (equal); Project administration (equal); Resources (equal); Software (equal); Supervision (equal); Validation (equal); Visualization (equal); Writing – original draft (equal); Writing – review & editing (equal). **Klaus Lehnertz:** Conceptualization (equal); Data curation (equal); Formal analysis (equal); Funding acquisition (equal); Investigation (equal); Methodology (equal); Project administration (equal); Resources (equal); Software (equal); Supervision (equal); Validation (equal); Visualization (equal); Writing – original draft (equal); Writing – review & editing (equal).

## DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## APPENDIX: ADDITIONAL FIGURES

Changes in rank for each constituent (with importance hierarchy prior to perturbation) in dependency on the rank of the targeted constituent in a small-world network (Fig. 5), a random network (Fig. 6), a scale-free network (Fig. 7), and a complete network (Fig. 8).

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# Impact of biological rhythms on the importance hierarchy of constituents in time-dependent functional brain networks

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Biological rhythms are natural, endogenous cycles with period lengths ranging from less than 24 h (ultradian rhythms) to more than 24 h (infradian rhythms). The impact of the circadian rhythm (approximately 24 h) and ultradian rhythms on spectral characteristics of electroencephalographic (EEG) signals has been investigated for more than half a century. Yet, only little is known on how biological rhythms influence the properties of EEG-derived evolving functional brain networks. Here, we derive such networks from multiday, multichannel EEG recordings and use different centrality concepts to assess the time-varying importance hierarchy of the networks' vertices and edges as well as the various aspects of their structural integration in the network. We observe strong circadian and ultradian influences that highlight distinct subnetworks in the evolving functional brain networks. Our findings indicate the existence of a vital and fundamental subnetwork that is rather generally involved in ongoing brain activities during wakefulness and sleep.

KEYWORDS

**functional brain network, vertex centrality, edge centrality, circadian rhythm, electroencephalographic signals**

## 1 Introduction

While describing natural complex dynamical systems is a notoriously difficult endeavor, the network approach (Boccaletti et al., 2006; 2014; Newman, 2018) has been repeatedly shown to provide novel and important insights into such systems in various research areas ranging from neurosciences (Bullmore and Sporns, 2009; Lehnertz et al., 2014) via genomics (Tyler et al., 2009) and proteomics (Uetz et al., 2000) to ecology (Hegland et al., 2009; Olesen et al., 2011; Delmas et al., 2019; Halekotte and Feudel, 2020), climatology (Donges et al., 2009; Zhou et al., 2015), and sociology (Onnela et al., 2007; Palla et al., 2007). This broad applicability is not least explained by the large manifold of network metrics, describing global aspects to local aspects in network terms, which in principle can be directly related to the properties of the described system. Identifying key network constituents is highly relevant when it comes to improving the understanding and control of networks, as it allows us to gain insights about the importance hierarchy of its constituents with respect to the network structure and dynamics. The characterization of a constituent's role in the network structure and dynamics can be achieved through different concepts and a growing number of metrics such as centralities. Most of these concepts focus on the description of vertices or groups of such [e.g., hubs (Newman, 2003), hub regions in the brain (Stanley et al., 2013; Chung, 2019), and k-core decompositions (Kong et al., 2019)], while only a few metrics assess the centrality of an edge. We recently proposed a novel strength-based edge-centrality concept (Bröhl and Lehnertz, 2022) and introduced modifications to vertex closeness and vertex eigenvector centrality concepts yielding corresponding edge centrality concepts (Bröhl and Lehnertz, 2019). We demonstrated that these edge centralities—together with edge betweenness centrality (Freeman, 1977; Girvan and Newman, 2002)—provide additional information about the network constituents for various topologies. These four centrality concepts, while different in their definition, can be considered complementary in the description of a constituent's structural integration in the network.

Many early studies assumed networks to be static; however, the recent paradigm shift toward time-dependent (or evolving) networks (Holme and Saramäki, 2012; Kivelä et al., 2014) allows one to describe many systems more accurately. This particularly holds true for biological networks, such as the brain, for which time dependencies on different scales have been observed. Both exogenous and endogenous biological rhythms are expected to assert influences on the level of the network description (Kuhnert et al., 2010; Lehnertz et al., 2017; Mitsis et al., 2020; Kurth et al., 2021; Lehnertz et al., 2021) and therefore on network metrics such as centralities (Geier et al., 2015; Geier and Lehnertz, 2017; Lehnertz et al., 2017; Lehnertz et al., 2021).

For more than 50 years, it has been known that the circadian rhythm and ultradian rhythms impact electroencephalographic (EEG) signals [see Lehnertz et al. (2021) for a recent overview]. Many former studies, however, were based on EEG recordings that either assessed the dynamics of few brain regions only or/and covered timescales ranging only from few seconds to hours. Here, we extend the recent studies and observations (Spoormaker et al., 2011; Chu et al., 2012; Park et al., 2012; Liu et al., 2015; Farahani et al., 2021) and investigate how biological rhythms, particularly the circadian rhythm (with a period length of approximately 24 h), influence the importance hierarchies of the constituents of evolving functional brain networks. Therefore, we focus on both the networks' vertices that are associated with the sampled brain regions and networks' edges that represent time-evolving interactions between brain regions.

# 2 Materials and methods

## 2.1 Data

We analyzed electroencephalographic signals obtained from eight subjects (three females, age 19–81 years) with (five subjects) and without disorders (three subjects) of the central nervous system (CNS). All subjects were under stable CNS medication (if taking any). The EEG data were recorded continuously over 4 to 8 days from 19 electrodes placed according to the 10–20 EEG system (Klem et al., 1999) (Cz served as a physical reference) with a sampling rate of 256 Hz, using a 16-bit analog-to-digital converter (Micromed, S.p.A., Mogliano Veneto, Italy). Data were band-pass filtered offline (bandwidth: 1–45 Hz; fourth-order Butterworth characteristic), and a notch filter (third order) was used to suppress contributions at the line frequency (50 Hz). Data used in this study were visually inspected to remove segments containing strong artifacts (e.g., subject movements or amplifier saturation).

## 2.2 Deriving evolving functional brain networks

Time-dependent, fully connected, weighted functional brain networks were constructed through a time-resolved synchronization analysis of an EEG recording (Mormann et al., 2000; Osterhage et al., 2007; Kuhnert et al., 2010; Goodfellow et al., 2022) to track the changes in the importance hierarchies of network constituents (Geier and Lehnertz, 2017; Rings et al., 2019; Fruengel et al., 2020) possibly related to biological rhythms (Lehnertz et al., 2021). To perform this, network vertices were associated with brain regions whose dynamics were sampled by electrodes and network edges were associated with time-varying estimates of the strength of interactions between the dynamics of the pairs of those brain regions, regardless of their anatomical connections. As an estimate of the strength of the interaction, we employed mean phase coherence ($R$) (Mormann et al., 2000), which assesses the degree of synchronization between two phase time series ($R = 1$ indicates fully phase-synchronized brain regions, and $R = 0$ indicates no phase synchronization). A non-overlapping sliding window with a duration of 20 s (5,120 data points) was used to calculate $R$ in a time-resolved manner. The chosen duration of a window can be considered a compromise between the required statistical accuracy for the calculation of $R$ and the approximate stationarity within the window's length (Lehnertz et al., 2017). For each window, we derived the instantaneous phase time series via the Hilbert transform of the EEG time series. An important property of this analytic signal approach (particularly in the case of two or more superimposed oscillatory components) is that the instantaneous frequency relates to the predominant frequency in the Fourier spectrum (Boashash, 1992). The predominant frequency may be subjected to fluctuations in the EEG time series. Thus, the instantaneous frequency can vary rhythmically around the predominant frequency, which results in spurious estimates of the instantaneous phase. By taking the temporal average, these effects can be reduced. From an electrophysiological point of view, we consider it more reasonable to look adaptively (e.g., via the Hilbert transform) at interactions between predominant rhythms in EEG rather than to look at interactions in some *a priori* fixed frequency bands (e.g., via wavelet transform) for which there is no power in the time series (Osterhage et al., 2007; Frei et al., 2010). Following these steps of analysis for each window, we end up with a temporal sequence of snapshot functional brain networks, each of which consists of $V$ vertices and $E$ edges and can be described by a weight matrix $\mathcal{W} \in [0,1]^{V\times V}$, where $\mathcal{W}_{ij}$ refers to the edge weight (strength of the interaction) between vertices $i$ and $j$. The number of actual windows per subject depended on the respective recording duration, thus yielding approximately 9,500–26,000 windows.

## 2.3 Estimating the importance of network constituents

In order to further investigate the temporal sequence of snapshot functional brain networks, different approaches may be adopted. Estimating distance or (dis-)similarity between two networks might be one such approach, although finding suitable distance metrics still remains a challenge (Mheich et al., 2020). Another approach consists of the so-far insufficiently studied concept of multilayer networks (De

Domenico, 2017). Yet, due to some fundamental limitations, a meaningful interpretation of multilayer brain networks remains to be explored (Buldú and Papo, 2018). Therefore, here, we pursue the investigation of the time series of networks' characteristics (Lehnertz et al., 2014; 2017) and utilize the following centrality metrics to estimate importance of each network's vertices and edges.

Strength centrality of a vertex $i$ is the sum of the weights of all edges connected to this vertex:

$$\mathcal{C}^{\mathrm{S}}_{\mathrm{v}}(i) = \sum_{j=0}^{V} \mathcal{W}_{ij}. \tag{1}$$

The higher the vertex's degree/strength, the more central it is considered to be. A related metric for edges is nearest-neighbor centrality, which considers an edge to be more central when its weight is larger and the strengths of the vertices that are connected by that edge are more similar and higher. Nearest-neighbor centrality of an edge $k$ between vertices $a$ and $b$ is defined as follows (Bröhl and Lehnertz, 2022):

$$\mathcal{C}^{\mathrm{S}}_{\mathrm{e}}(k) = \frac{\mathcal{C}^{\mathrm{S}}_{\mathrm{v}}(a) + \mathcal{C}^{\mathrm{S}}_{\mathrm{v}}(b) - 2w_k}{|\mathcal{C}^{\mathrm{S}}_{\mathrm{v}}(a) - \mathcal{C}^{\mathrm{S}}_{\mathrm{v}}(b)| + 1}\, w_k, \tag{2}$$

where $k \in \{1, \ldots, E\}$, $(a, b) \in \{1, \ldots, V\}$, and $w_k = \mathcal{W}_{ab}$ denotes the weight of edge $k$ connecting vertices $a$ and $b$. Similar to strength centrality of a vertex, nearest-neighbor centrality of an edge is only influenced by its adjacent constituents. Hence, vertices (brain regions) and edges (interactions between pairs of brain regions) that have high $\mathcal{C}^{\mathrm{S}}$ values are largely interconnected with the neighboring vertices and edges. When structurally viewed, these neighboring constituents would be located in either the same areas of the brain or an adjacent area; from a functional perspective, they might be associated with any area of the brain. Hence, constituents with high $\mathcal{C}^{\mathrm{S}}$ values are highly interconnected within the functional network, although not necessarily allowing a structural interpretation.

Eigenvector centrality considers the influence of a vertex/edge on the network as a whole, where a vertex/edge is considered central if the vertex/edge adjacent to it is also central, and it is defined as

$$\mathcal{C}^{\mathrm{E}}_{\mathrm{v,e}}(i) = \frac{1}{\lambda_{\max}} \sum_{l} M_{il}\, \mathcal{C}^{\mathrm{E}}_{\mathrm{v,e}}(l). \tag{3}$$

In case of vertices, $(i, l) \in \{1, \ldots, V\}$ and $\mathbf{M}$ denotes the weight matrix $\mathcal{W}^{(\mathrm{v})} \in [0,1]^{V\times V}$, where $\mathcal{W}^{(\mathrm{v})}_{il}$ denotes the weight of an edge between vertices $i$ and $l$. We define $\mathcal{W}^{(\mathrm{v})}_{ii} := 0\,\forall\, i$ with $i \in \{1, \ldots, V\}$. In the case of edges, $(i, l) \in \{1, \ldots, E\}$ and $\mathbf{M}$ denotes the weight matrix $\mathcal{W}^{(\mathrm{e})} \in [0,1]^{E\times E}$, whose entries $\mathcal{W}^{(\mathrm{e})}_{il}$ are assigned to the average weight of edges $i$ and $l$, if these edges are connected to the same vertex, and 0 otherwise. As mentioned previously, we define $\mathcal{W}^{(\mathrm{e})}_{ii} := 0\,\forall\, i$ with $k \in \{1, \ldots, E\}$. Equation 3 is applied iteratively until eigenvector centrality values remain stable. Hence, eigenvector centrality can be considered a strength-based centrality concept, which, due to its recursive definition, relates a vertex/edge to all the other vertices/edges in the network. Similar to strength/nearest-neighbor centrality, constituents with high $\mathcal{C}^{\mathrm{E}}$ values are gradiently stronger connected to closer constituents than to those that are far off. Again, distance-related descriptions, such as "close" or "far-off," relate to the functional network and, hence, do not necessarily allow a structural interpretation, meaning constituents with large $\mathcal{C}^{\mathrm{E}}$ values are highly connected to the functional network in a rather general sense. This high inter-connectedness refers to many and/or possibly strong interactions with constituents either associated with the same brain area or possibly with any other area.

Closeness centrality considers the distance between a vertex/edge and all the other vertices/edges in the network. A vertex/edge with high closeness centrality is considered central as information obtained from this vertex/edge can reach all the other constituents in the network via short paths and so the vertex/edge can exert a more direct influence on the network. Closeness centrality of vertex $k$ is defined as (Bavelas, 1950)

$$\mathcal{C}^{\mathrm{C}}_{\mathrm{v}}(n) = \frac{V-1}{\sum_m d_{nm}}, \tag{4}$$

where $(n, m) \in \{1, \ldots, V\}$ and $d_{nm}$ represents the length of the shortest path between vertices $n$ and $m$, which is calculated as the sum of the inverse of all edge weights on the path. Closeness centrality of edge $k$ between vertices $a$ and $b$ can be defined as (Bröhl and Lehnertz, 2019)

$$\begin{aligned}\mathcal{C}^{\mathrm{C}}_{\mathrm{e}}(k) &= \frac{E-1}{\sum_i (d_{ia} + d_{ib})} = \frac{E-1}{\dfrac{1}{\mathcal{C}^{\mathrm{C}}_{\mathrm{v}}(a)} + \dfrac{1}{\mathcal{C}^{\mathrm{C}}_{\mathrm{v}}(b)}}\\ &= (E-1)\frac{\mathcal{C}^{\mathrm{C}}_{\mathrm{v}}(a)\mathcal{C}^{\mathrm{C}}_{\mathrm{v}}(b)}{\mathcal{C}^{\mathrm{C}}_{\mathrm{v}}(a) + \mathcal{C}^{\mathrm{C}}_{\mathrm{v}}(b)},\end{aligned} \tag{5}$$

where $k \in \{1, \ldots, E\}$ and $(a, b, i) \in \{1, \ldots, V\}$. Hence, closeness centrality can be considered a path-based centrality concept, which is therefore influenced by the network as a whole. High closeness centrality points toward a constituent, which is associated with any brain area that is functionally "close" to any other constituent associated with any brain area. Hence, certain parts (with high $\mathcal{C}^{\mathrm{C}}$) of certain brain areas interact strongly with many other parts in the same area, while also interacting with many other brain areas.

Betweenness centrality is a measure of how frequently the shortest path traverses a given vertex/edge. A vertex/edge with high betweenness centrality is considered central because it acts as a bridge between other brain regions. Vertex/edge betweenness centrality (of vertex/edge $i$) can be defined as (Freeman, 1977; Brandes, 2001; Girvan and Newman, 2002)

$$\mathcal{C}^{\mathrm{B}}_{\mathrm{v,e}}(i) = \frac{2}{F} \sum_{n\neq m} \frac{q_{nm}(i)}{G_{nm}}, \tag{6}$$

where $i \in \{1, \ldots, V\}$, $i \in \{1, \ldots, E\}$, and $\{n, m\} \in \{1, \ldots, V\}$; $q_{nm}(i)$ represents the number of shortest paths between vertices $n$ and $m$ running through vertex/edge $i$, and $G_{nm}$ represents the total number of shortest paths between vertices $n$ and $m$. The length of a path is calculated as the sum of the inverse of all edge weights on that path. The normalization factor is given as $F = (V{-}1)\ (V{-}2)$ in the case of vertices and $F = V(V{-}1)$ in the case of edges. Hence, betweenness centrality can be considered a path-based centrality concept, which is therefore influenced by the network as a whole. Constituents with high betweenness centrality are likely to be part of bottleneck-like structures spanning between brain areas, both in a structural and functional sense.

In order to facilitate a qualitative comparision of the results obtained with the different centrality concepts, we utilized centrality value-based importance ranking of constituents (Liao et al., 2017). A vertex/edge with the largest centrality value gets assigned to rank 1. The rank increases in increments of 1 for the vertex/edge with the second largest centrality value, third largest centrality value, etc., yielding an increasing rank as the centrality values decrease. This

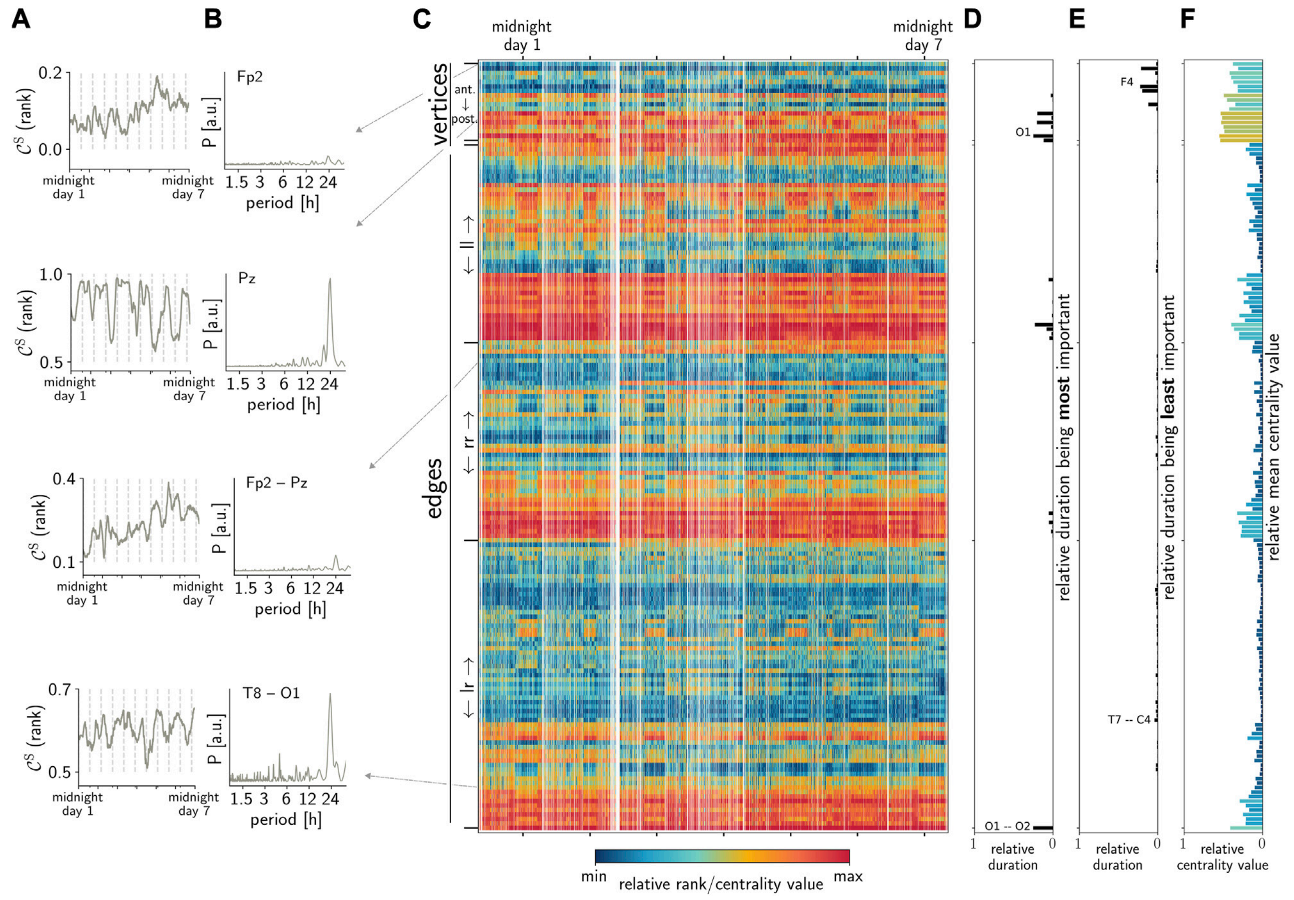

FIGURE 1
Exemplary observations: **(A)** temporal sequences of the importance of arbitrarily chosen vertices (here, FP2 and PZ) and edges (FP2–PZ and T8–O1) estimated with $\mathcal{C}_{\mathrm{v}}^{\mathrm{S}}$ and $\mathcal{C}_{\mathrm{e}}^{\mathrm{S}}$, respectively. **(B)** Lomb–Scargle periodograms of sequences in **(A)**. **(C)** Temporal evolution of the relative rank (color-coded) of all network constituents (ant., anterior; post., posterior; ll, left-hemispheric interactions; rr, right-hemispheric interactions; lr, inter-hemispheric interactions; white vertical lines depict recording gaps). Electrode contacts are displayed in the following descending order (top to bottom) respectively: ant. – post.: Fp1, Fp2, F7, F3, Fz, F4, F8, T7, C3, C4, T8, P7, P3, Pz, P4, P8, O1, O2; ll: Fp1-F7, Fp1-F3, Fp1-Fz, Fp1-T7, Fp1-C3, Fp1-P7, Fp1-P3, Fp1-Pz, Fp1-O1, F7-F3, F7-Fz, F7-T7, F7-C3, F7-P7, F7-P3, F7-Pz, F7-O1, F3-Fz, F3-T7, F3-C3, F3-P7, F3-P3, F3-Pz, F3-O1, Fz-T7, Fz-C3, Fz-P7, Fz-P3, Fz-O1, T7-C3, T7-P7, T7-P3, T7-Pz, T7-O1, C3-P7, C3-P3, C3-Pz, C3-O1, P7-P3, P7-Pz, P7-O1, P3-Pz, P3-O1, Pz-O1; rr: Fp2-Fz, Fp2-F4, Fp2-F8, Fp2-C4, Fp2-T8, Fp2-Pz, Fp2-P4, Fp2-P8, Fp2-O2, Fz-F4, Fz-F8, Fz-C4, Fz-T8, Fz-P4, Fz-P8, Fz-O2, F4-F8, F4-C4, F4-T8, F4-Pz, F4-P4, F4-P8, F4-O2, F8-C4, F8-T8, F8-Pz, F8-P4, F8-P8, F8-O2, C4-T8, C4-Pz, C4-P4, C4-P8, C4-O2, T8-Pz, T8-P4, T8-P8, T8-O2, Pz-P4, Pz-P8, Pz-O2, P4-P8, P4-O2, P8-O2; lr: Fp1-Fp2, Fp1-F4, Fp1-F8, Fp1-C4, Fp1-T8, Fp1-P4, Fp1-P8, Fp1-O2, Fp2-F7, Fp2-F3, Fp2-T7, Fp2-C3, Fp2-P7, Fp2-P3, Fp2-O1, F7-F4, F7-F8, F7-C4, F7-T8, F7-P4, F7-P8, F7-O2, F3-F4, F3-F8, F3-C4, F3-T8, F3-P4, F3-P8, F3-O2, Fz-Pz, F4-T7, F4-C3, F4-P7, F4-P3, F4-O1, F8-T7, F8-C3, F8-P7, F8-P3, F8-O1, T7-C4, T7-T8, T7-P4, T7-P8, T7-O2, C3-C4, C3-T8, C3-P4, C3-P8, C3-O2, C4-P7, C4-P3, C4-O1, T8-P7, T8-P3, T8-O1, P7-P4, P7-P8, P7-O2, P3-P4, P3-P8, P3-O2, P4-O1, P8-O1, O1-O2. **(D,E)** Fraction of the recording time during which a respective constituent was the most/least important. **(F)** Average relative centrality values ($\mathcal{C}_{\mathrm{v}}^{\mathrm{S}}$ and $\mathcal{C}_{\mathrm{e}}^{\mathrm{S}}$, respectively, normalized to the maximum value) over the recording time.

ranking can be further normalized, yielding a relative ranking with the highest relative rank being 1 (most important) and the lowest relative rank being 0 (least important). Hence, we can deduce an importance hierarchy for the vertices and edges of each snapshot functional brain network.

## 2.4 Characterizing the influence of biological rhythms on the importance of network constituents

The aforementioned steps of analysis provide us with a temporal sequence of vertex/edge importance hierarchies of an evolving functional brain network and enable the investigation of how biological rhythms impact this hierarchy. To this end, we proceed as described in Lehnertz et al. (2021) and estimate the power spectral densities [Lomb–Scargle periodogram (Press et al., 1989)] of the respective temporal sequences. Eventually, we quantified the influence of the circadian rhythm on each such sequence as the portion of power for period lengths in the range of 20–28 h relative to the total power in the range of 1–36 h. We refer to this ratio as $P_{24}$ in the following sections.

# 3 Results

We observe contributions of rhythms with period lengths of approximately 24 h (and to a lesser extent from rhythms of

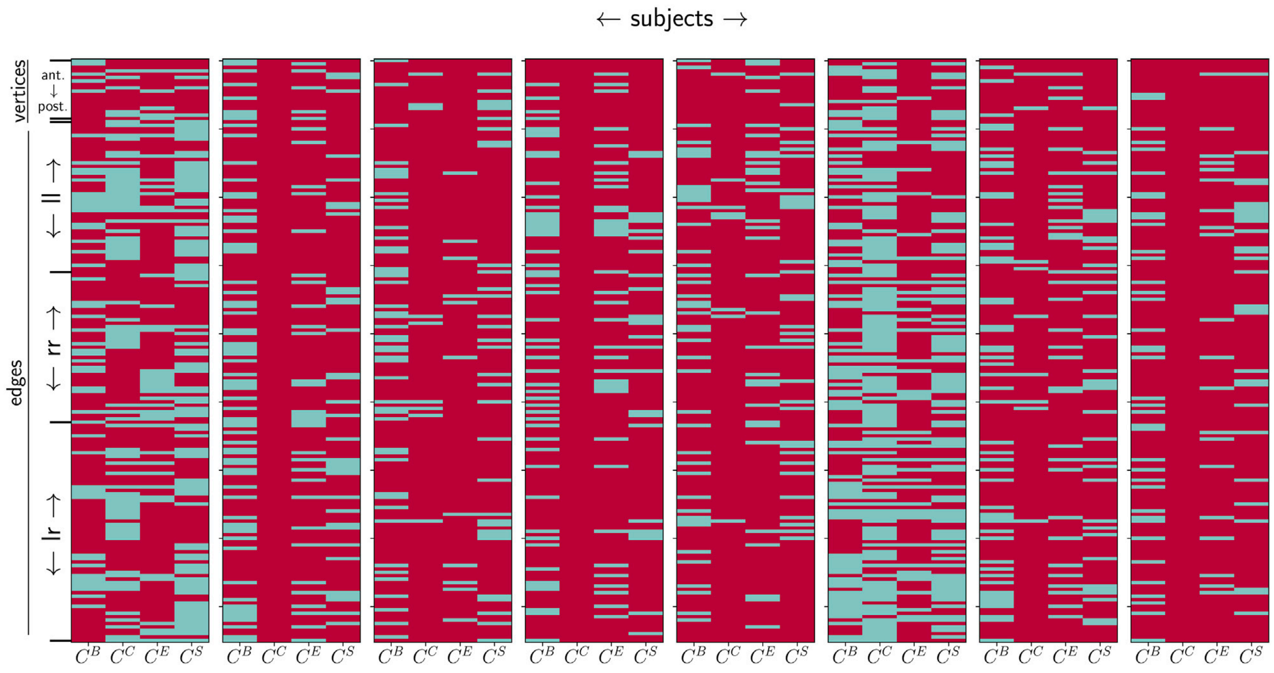

FIGURE 2
Influence of the circadian rhythm (estimated with $P_{24}$) on centrality values of network constituents (assessed with betweenness centrality $\mathcal{C}^B$, closeness centrality $\mathcal{C}^C$, eigenvector centrality $\mathcal{C}^E$, and strength/nearest-neighbor centrality $\mathcal{C}^S$). Pale blue: $P_{24} \le 0.5$; red: $P_{24} > 0.5$.

approximately 12 h or shorter) in all temporal sequences of importance (centrality values and ranks) of the respective network constituents from each subject. However, and contrary to the expectation, we found that these circadian and ultradian contributions are more pronounced in the sequences of some vertices and edges, i.e., some brain regions, as well as the interactions between their dynamics (see Figure 1).

Interestingly, we also observe that the strength of circadian contributions differs for temporal sequences derived with different centrality metrics. This is to be expected, at least to some extent, since the metrics highlight different structural aspects of a network, such as the path-structure or strength distribution. Nevertheless, these observations suggest that the circadian rhythm affects these different structural aspects. Figure 2 demonstrates that this rather unspecific relation regarding path/strength-based centrality metrics for vertices and edges can be observed in the data from all the investigated subjects. Moreover, it becomes quite apparent from this figure that by combining the results yielded by different centrality concepts, almost all network constituents are impacted by the circadian rhythm in all subjects.

Yet, it can also be observed that there is no trivial relation between the influence of the circadian rhythm (estimated with $P_{24}$) and a constituent's importance (*cf.* Figure 3). Neither for the most nor for the least important network constituents do we observe a generally specific influence of the circadian rhythm (as well as for ultradian rhythms (data not shown)).

Furthermore, we find that different centrality metrics identify different constituents as the most important (on average over the whole observation time, in line with previous studies) (see, e.g., Kuhnert et al. (2012); Bröhl and Lehnertz (2019); Bröhl and Lehnertz (2022); and the references therein). One needs to take into account that the constituents deemed the most important on average do not always coincide with the constituents that are deemed the most important for the largest fraction of the recording time (*cf.* Figure 4). Likewise, constituents, for which the temporal profiles of importance are impacted strongly by the circadian rhythm, neither coincide with those constituents that are deemed the most important on average nor with those constituents that are deemed the most important for most of the recording time. This discrepancy cannot be traced back to the ceiling or floor effects, resulting from the definitions of their respective centrality metrics. Overall, we observe a rather unspecific influence of primarily the circadian rhythm on many structural aspects of network constituents: each brain region (vertex) and even interactions between such regions (edges) appear to be influenced, at least to some extent, in their structural integration.

In order to improve on the findings achieved so far, we investigate whether there exists a day/night pattern in the temporal evolution of the importance of vertices and edges (*cf.* Figures 1A, C). Interestingly, we observe that the largest differences in the importance of network constituents between night- and daytimes are related to very distinct brain areas along with their interactions (see Figure 5). These vertices and edges not only exhibit the largest change in centrality values when functional brain networks transit from night- to daytimes but are also further identified as the most important constituent on average and for

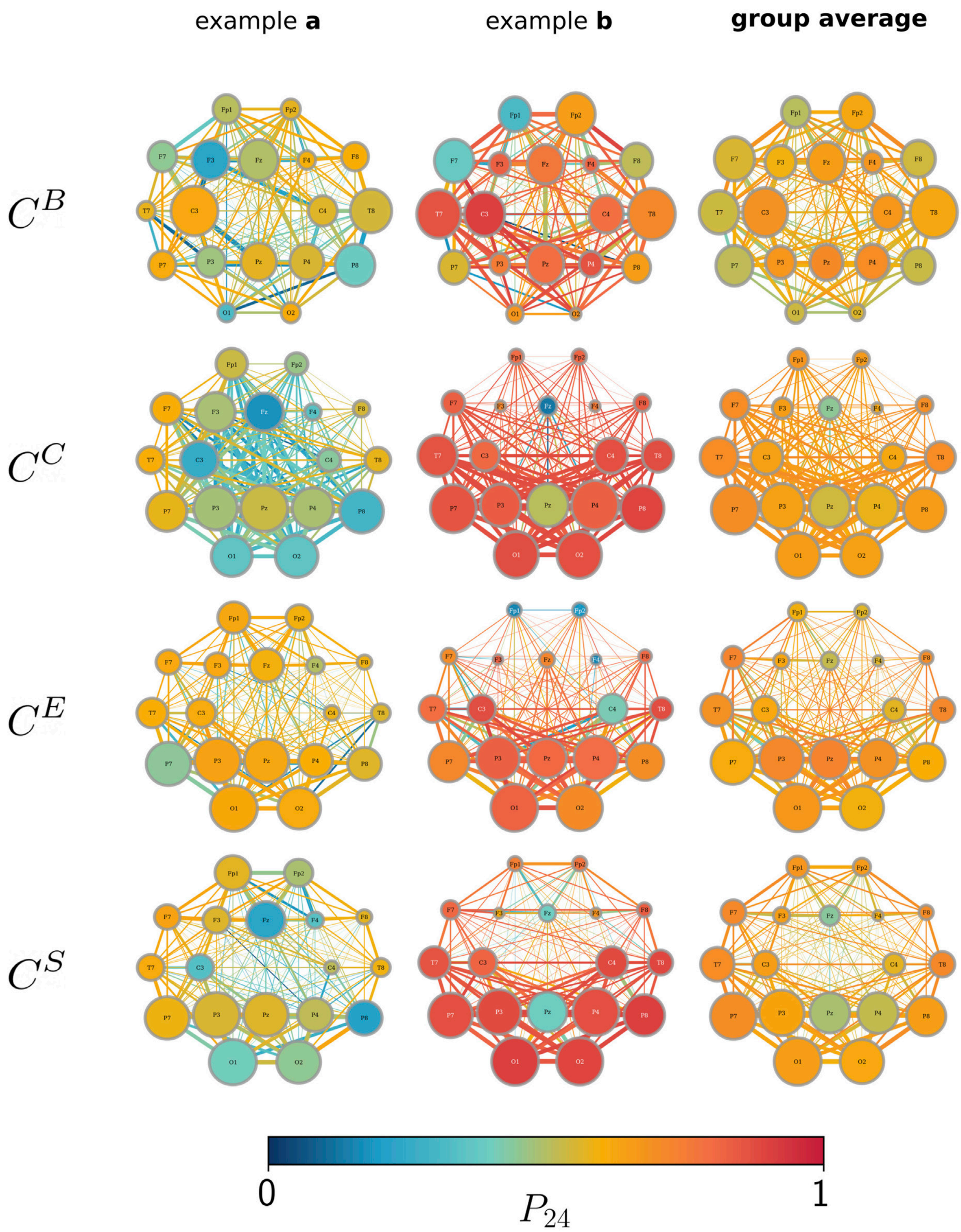

FIGURE 3
Influence of the circadian rhythm ($P_{24}$; color-coded) and the average importance over the recording time (the size of vertices/edges; the larger they are, the more important they are). Importance estimated with betweenness centrality $\mathcal{C}^B$, closeness centrality $\mathcal{C}^C$, eigenvector centrality $\mathcal{C}^E$, and strength/nearest-neighbor centrality $\mathcal{C}^S$. Networks are depicted in the layout of the 10–20 EEG system (Klem et al., 1999). Examples a and b (left and middle columns) represent the observed opposing extreme cases from two subjects, either showing an overall little (example a) or strong (example b) influence of the circadian rhythm. The right column shows the group average over all the subjects.

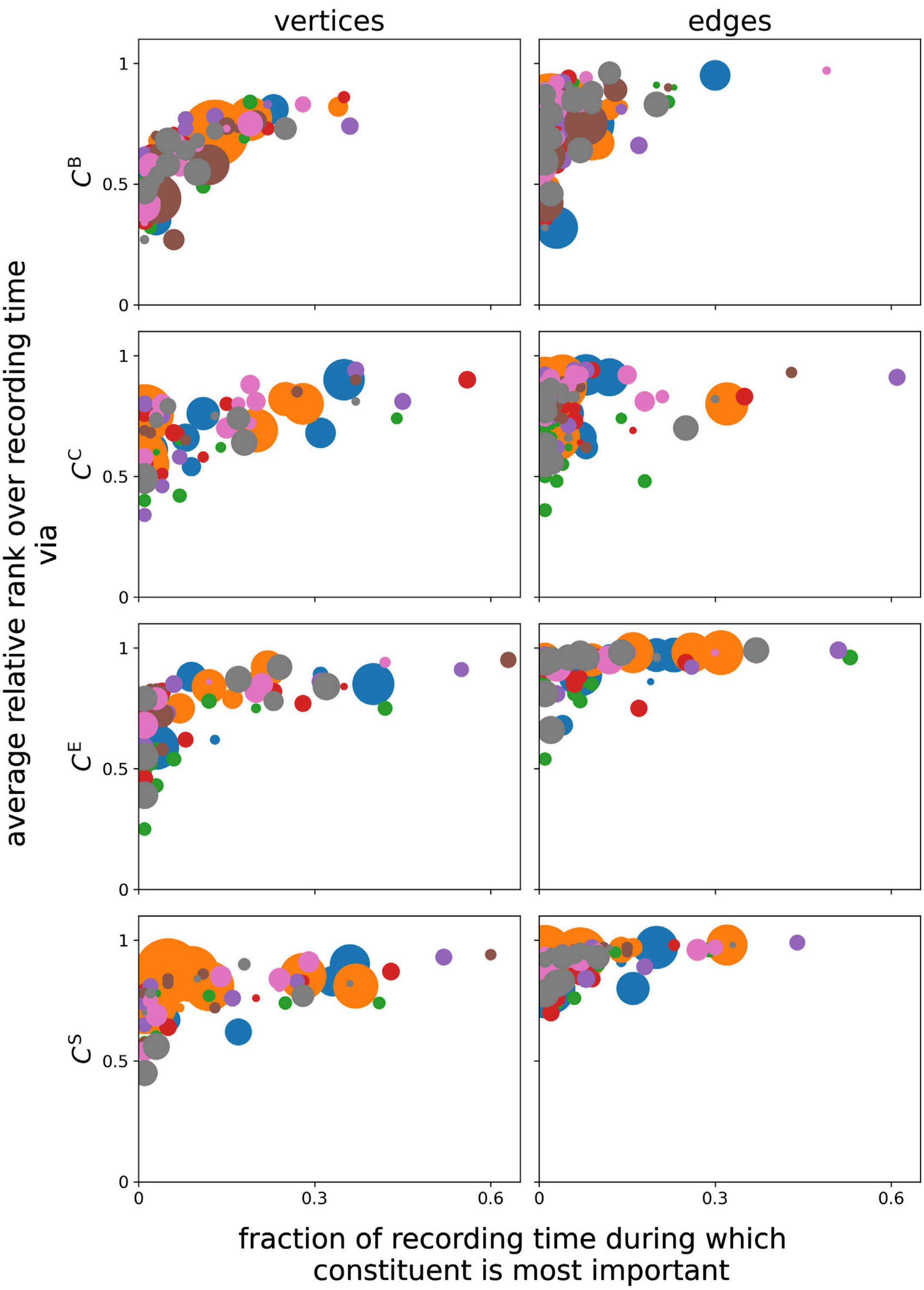

FIGURE 4
Relation between constituents' average relative rank over the total recording time and their fraction of the recording time, for which the constituents are deemed the most important. Marker colors encode the different subjects, and marker sizes encode the relative power corresponding to the 24-h peak related to the circadian rhythm.

the largest fraction of the total recording time. While betweenness centrality highlights bilateral frontotemporal vertices and edges, closeness centrality highlights the predominantly left temporoparietal vertices and edges. Both strength-based centralities (eigenvector centrality and nearest-neighbor centrality) predominantly highlight the left temporoparietal and

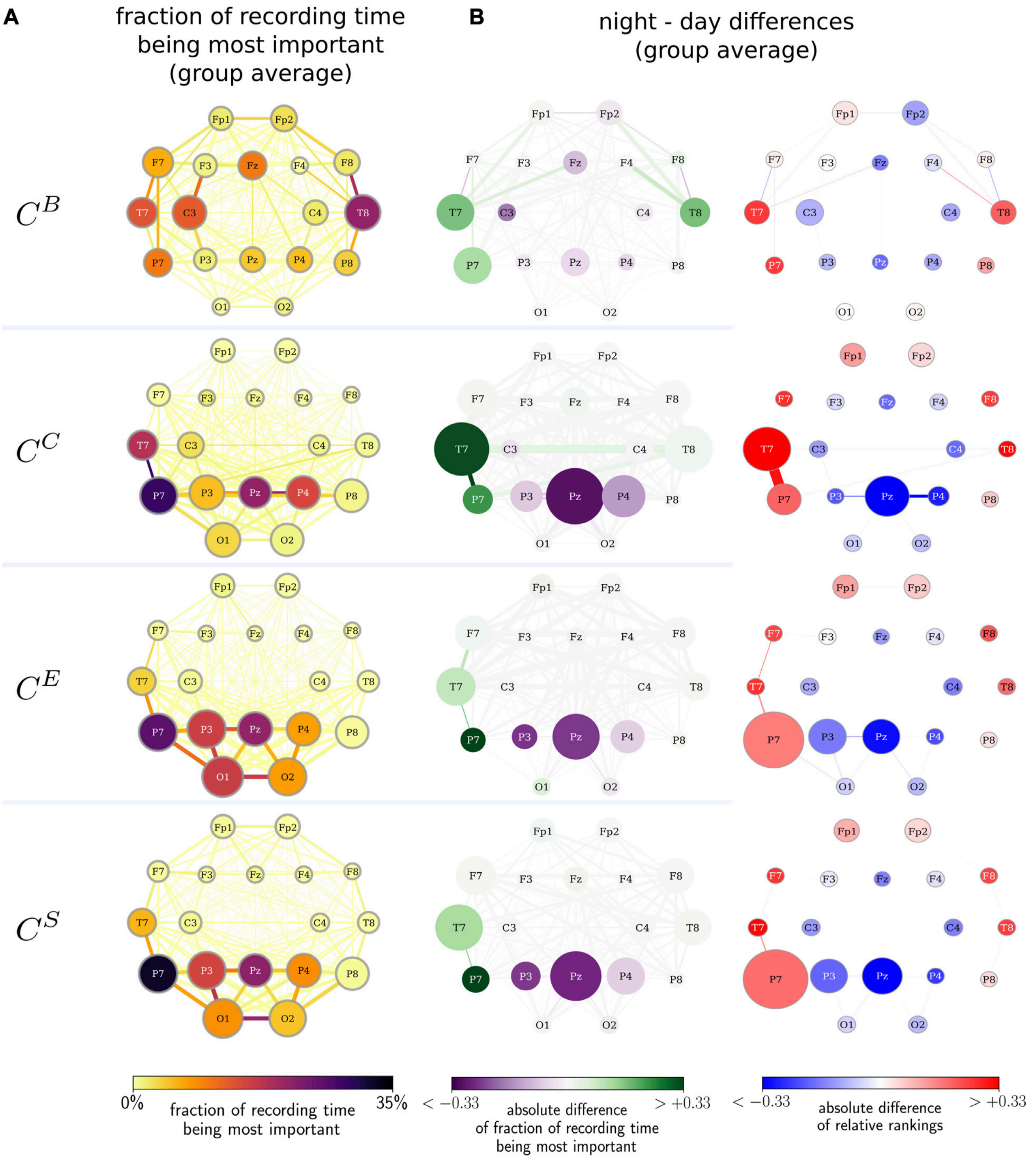

FIGURE 5
**(A)** Fraction of the recording time during which a network constituent is the most important (color-coded) and the average relative rank of the constituent (size-coded). Importance assessed with betweenness centrality $\mathcal{C}^B$, closeness centrality $\mathcal{C}^C$, eigenvector centrality $\mathcal{C}^E$, and strength/nearest-neighbor centrality $\mathcal{C}^S$. Middle column: Absolute night–day differences in the fraction of the recording time during which the respective constituent is the most important (color-coded, green/purple indicating a higher fraction of the recording time during night/day) and the absolute value of the absolute difference in the constituents' relative rankings (size-coded). **(B)** Absolute night–day difference in constituents' relative rankings (color-coded, red/blue indicating a higher relative ranking during night/day) and the absolute value of the absolute difference in the fraction of the recording time during which a network constituent is the most important (size-coded). The respective data are averaged over all subjects and their respective night/day periods.

left parietooccipital vertices and edges. Independent of the employed centrality metric, temporoparietal network constituents (vertices T7, T8, and P7 as well as their associated edges) are identified as the most important during daytime (here, 12:00 to 16:00 h). In contrast, during nighttime (here, 24:00 to 4:00 h), the importance shifts to parietal network constituents (vertices P3, P4, and PZ as well as their associated edges). Apart from this night–daytime-related spatial shift of the importance of a few network components, our findings also point toward a key arrangement of connected vertices and edges, relating to a subnetwork that comprises vertices T7, P7, P3 PZ, and P4 together with their associated edges. This subnetwork, which is slightly more dominantly located on the left brain hemisphere, is possibly involved in ongoing activities during wakefulness and sleep.

## 4 Discussion

We investigated how the circadian rhythm impacts the time-dependent importance hierarchy of the vertices and edges of an evolving functional brain network. We employed different path- and strength-based centrality metrics for vertices and edges to comprehensively characterize the importance hierarchy of these network constituents. At the single-constituent level, we observed that their time-dependent changes in importance are clearly modulated by the circadian rhythm although to a varying degree. Irrespective of their interindividual variabilities, we observed pronounced differences in the constituents' importance hierarchy when contrasting data obtained during daytimes and nighttimes. This may point to a local, circadian rhythm-driven modulation of the dynamics of various brain regions alongside their interactions. These brain regions form vital and fundamental subnetworks within the evolving functional brain networks.

The subnetwork highlighted with betweenness centrality comprises temporofrontal brain regions from both hemispheres. It is rather unexpected that the subnetworks, as highlighted with closeness, eigenvector, and strength/nearest-neighbor centrality metrics (but not with betweenness centrality), are largely overlapping, despite the fact that the different centrality metrics assess different structural aspects of network constituents. This subnetwork is predominantly restricted to the temporoparietal brain regions, with a left-hemispheric dominance during the nighttime. However, whether the subnetworks observed here are related to the resting-state network needs further investigation (Raichle, 2015).

Studies revealed that the hippocampus, deep inside the temporal lobe, and the visual cortex are simultaneously involved in the reactivation of coherent memory traces during sleep, which points toward a contribution to the memory consolidation process (Prabhakaran et al., 2000; Albouy et al., 2013). The interaction between those brain regions might possibly relate to the T7–P7 (–T8) structure in the observed vital subnetworks as these vertices and edges, associated with these electrodes and interactions between the sampled brain regions, are deemed more important in general and for a larger fraction of time during the nighttime compared to the daytime.

During the daytime, the vertices and edges associated with the parietal lobes (PZ, P3, and P4) are deemed more important and for a larger fraction of time compared to the nighttime. These areas consolidate spatial and visual information and integrate perceptions with other sensory inputs, resulting in the recognition of the trajectories of moving objects. These areas also mediate proprioception (perception of the position of the body in space) and are involved in skills such as arithmetic, writing, left–right orientation, and finger perception (see Rizzolatti et al. (1997) for an overview). Since these functions may also be involved during dream phases (which account for approximately 25% of the sleep period), these vertices and edges are nonetheless important during nighttimes although for shorter periods of time.

Overall, we observe that circadian (and ultradian) biological rhythms strongly influence the importance hierarchy, as assessed with different centrality concepts, of the constituents in time-dependent functional brain networks. These observations highlight, for each employed centrality concept, distinct subnetworks in evolving functional brain networks. The structural composition of these networks, however, largely coincides, which points toward the existence of a vital and fundamental subnetwork that is rather generally involved in ongoing brain activities.

## Data availability statement

The data analyzed in this study are subject to the following licenses/restrictions: the datasets presented in this article are not readily available because they contain information that could compromise the privacy of research participants. Requests to access the datasets should be directed to the corresponding author.

## Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the University of Bonn. The patients/participants provided their written informed consent to participate in this study.

## Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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## Conflict of interest

The authors RvW and KL declared that they were editorial board members of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note

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Chaos

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## ABSTRACT

The collective dynamics of complex networks of FitzHugh–Nagumo units exhibits rare and recurrent events of high amplitude (extreme events) that are preceded by so-called proto-events during which a certain fraction of the units become excited. Although it is well known that a sufficiently large fraction of excited units is required to turn a proto-event into an extreme event, it is not yet clear how the other units are being recruited into the final generation of an extreme event. Addressing this question and mimicking typical experimental situations, we investigate the centrality of edges in time-dependent interaction networks. We derived these networks from time series of the units' dynamics employing a widely used bivariate analysis technique. Using our recently proposed edge-centrality concepts together with an edge-based network decomposition technique, we observe that the recruitment is primarily facilitated by sets of certain edges that have no equivalent in the underlying topology. Our finding might aid to improve the understanding of generation of extreme events in natural networked dynamical systems.

**Many natural, technological, or social systems are capable of recurrently generating large events that can lead to disasters when interacting with exposed or vulnerable human or natural systems. The understanding of the dynamical underpinnings of the generation of such extreme events has recently attracted much attention. While certain dynamical mechanisms have already been identified, only little is know about potential pathways in networked dynamical systems, which may play a vital role in facilitating the build-up of precursor structures that eventually lead to an extreme event. We here use the concept of centrality—originally proposed in the social sciences for network vertices and recently extended for network edges—to identify such pathways in networks of coupled, weakly interacting nonlinear oscillators. These networks are prototypical for excitable systems and are capable of self-generating and self-terminating extreme events. We demonstrate that particularly interactions and only rarely edges in the coupling topology facilitate the build-up of precursor structures of extreme events.**

## I. INTRODUCTION

Extreme weather events and other natural hazards, large-scale blackouts in power supply networks, market crashes, mass panics, wars, harmful algal blooms in marine ecosystems, or epileptic seizures in the human brain are recurrent, large-impact events that occur spontaneously in many natural, technological, or social dynamical systems.[1–7] For systems that can be described by a time-dependent (or evolving) interaction network, novel methods have been developed over the last years that allow one to identify precursors of extreme events.[8] This holds true particularly for climate extremes,[9–20] seismic extremes,[21] hydrological extremes,[22] economic extremes,[23–25] and epileptic seizures.[26,27] Methods employed so far either aim at assessing global networks properties (e.g., clustering-coefficient-related or path-related measures) or local network properties—mostly vertex centralities.[28] For interaction networks—in which an edge represents attributes of an interaction (strength, direction, coupling function) between two vertices—an improved characterization of edge properties could add to advance understanding, prediction, and control of such networks.[29] To this end, and in order to find which edges in a network are important between other pairs of vertices, we recently modified various, widely used centrality concepts for vertices to those for edges.[30] We also proposed a network decomposition technique that is based on edge centrality and allows one to identify a hierarchy of sets of edges with each set being associated with a different level of importance.[30]

We here apply these novel concepts to investigate precursor structures of extreme events in the dynamics of complex networks of excitable units of FitzHugh–Nagumo type. Previous studies[31–35] have shown these systems to be capable of self-generating and self-terminating strong, rare, short-lasting, and recurrent deviations from their regular dynamics without the influence of noise or parameter change. These extreme events are preceded by local excitations (so-called proto-events[31,35]) in a certain fraction of units that play a decisive role in their generation. Similar phenomena were also observed in other excitable systems.[36–45] It is, however, not yet clear how the other units in a network are being recruited into the final generation of an extreme event, and we here conjecture that the recruitment is facilitated by certain edges. We demonstrate the suitability of our novel concepts for the analysis of empirical data by mimicking typical experimental situations.

## II. METHODS

### A. Networks of excitable units

We consider networks of $V$ diffusively coupled, excitable FitzHugh–Nagumo units ($n \in \{1, \ldots, V\}$), where the equations of motion of unit $n$ read

$$\dot{x}_n = x_n(a_n - x_n)(x_n - 1) - y_n + \frac{K}{V-1}\sum_{m=1}^{V} A_{nm}(x_m - x_n),$$
$$\dot{y}_n = b_n x_n - c_n y_n. \tag{1}$$

The unit's internal control parameters are $a_n$, $b_n$, and $c_n$, and the coupling strength is denoted by $K$. The symmetric adjacency matrix $\boldsymbol{A} \in \{0,1\}^{V\times V}$ has entries $A_{nm} = A_{nm} = 1$, iff units $n$ and $m$ are coupled. We employ parameter settings that had been identified in previous studies[31,32,35] to allow robust generation of extreme events in complex networks. In particular, we set parameters $a$ and $c$ identical for all units: $a_n = a = 0.0274\,\forall n$ and $c_n = c = 0.018\,\forall n$; the parameter $b$ is mismatched with $b_n = 0.006 + \frac{n}{V-1}0.008, \forall n$, and the coupling strength $K$ is chosen individually for each network. We regard three coupling topologies each of which connects $V = 20$ vertices but with different number of edges $E$:

- $\mathrm{T_A}$: a binary network with a small-world topology[46] with $E = 100$ (number of nearest neighbors: 5; rewiring probability: 0.25) and $K = 0.128$.
- $\mathrm{T_B}$: a binary network with a small-world topology[46] with $E = 40$ (number of nearest neighbors: 2; rewiring probability: 0.25) and $K = 0.33$.
- $\mathrm{T_C}$: a binary network with a scale-free topology[47] with $E = 36$ and $K = 0.1128$. The degree ($\kappa$) distribution $\mathcal{F}$ of the network follows a power law of the form $\mathcal{F}(\kappa) \propto \kappa^{-3}$.

Each networks' dynamics was integrated using an adaptive, explicit Runge–Kutta method of fifth order[48] with a step size of 11. We discarded at least $10^4$ initial time units, and time series (here: $x$-components) used for further analyses consisted of $10^6$ data points. The choice of the initial conditions (near the attractor) had no influence on our observations.

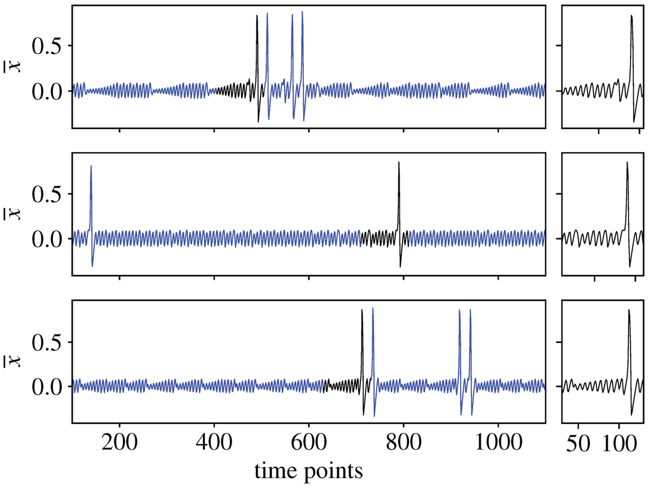

**FIG. 1.** (Left) Exemplary temporal evolutions of the average of the first dynamical variable $\bar{x}$ for topologies $\mathrm{T_A}$–$\mathrm{T_C}$ (top to bottom). (Right) Excerpt around an extreme event (colored black) of the respective time series.

In Fig. 1, we show, for each coupling topology, excerpts of the time series of the average of the first dynamical variable $\bar{x}(t) = \frac{1}{V}\sum_n^V x_n(t)$. Generally, we observe $\bar{x}(t)$ to exhibit irregular, low-amplitude oscillations[31,32,35] with $-0.15 < \bar{x}(t) < 0.15$. Occasionally, we observe stereotyped events at which all units become excited and thus $\bar{x}(t)$ clearly exceeds—by at least a factor of six—the amplitude of the collective low-amplitude oscillations. We consider these rare but recurring high-amplitude events as extreme events [time interval beginning with $\bar{x}(t)$ exceeding a threshold $\theta = 0.5$]. We find 195 such events for $\mathrm{T_A}$, 138 events for $\mathrm{T_B}$, and 830 events for $\mathrm{T_C}$. For $\mathrm{T_A}$ and $\mathrm{T_C}$, for which we often observe double extreme events,[31,35] only the leading one is considered.

### B. Data-driven construction of time-dependent interaction networks

Mimicking typical experimental situations,[49–52] we derive time-dependent interaction networks by estimating—using a sliding-window approach—the strength of interaction between pairs $\{n, m\} \in \{1, \ldots, V\}$ of time series of the first dynamical variable $x$. To do so, we employed an established method for investigating time-variant changes in phase synchronization. The mean phase coherence[53] is defined as

$$R_{nm} = \left| \frac{1}{T}\sum_{t=0}^{T-1} e^{i(\Phi_n(t) - \Phi_m(t))} \right|, \tag{2}$$

where $\Phi_n$ are the instantaneous phases of time series from unit $n$ (we here use the Hilbert transform[53,54]) and $T$ denotes the number of data points. By definition, $R_{nm}$ is confined to the interval [0,1], where $R_{nm} = 1$ indicates fully phase-synchronized units. Note that the window size $T$ is a critical parameter since it affects the sensitivity of the mean phase coherence. We here chose $T$ such that a window captured at least one full cycle of either an extreme event or a low-amplitude oscillation.

Having calculated $R_{nm}$ for all pairs $(n, m)$ of units, we derived—for each window—a synchronization matrix whose non-diagonal elements were associated with an adjacency matrix $\tilde{\mathbf{A}}$. This matrix represents an undirected, weighted snapshot network. To simplify notation, in the following we define $\tilde{A}_{nn} := 0\,\forall\, n$. Depending on the underlying coupling topology we refer to these time-dependent interaction networks as networks A, B, and C.

We position a reference window (window number 0) around the extreme event such that the window center coincides with the first time point for which the amplitude of $\overline{x}(t)$ exceeds the threshold $\theta$. The window number increases while going back in time with time windows of number 6 or larger are assumed to represent typical inter-event dynamics.

## C. Estimating edge importance in time-dependent interaction networks

For our investigations, we employ two opposing[30] concepts to estimate the centrality of edges in each snapshot network, namely, edge betweenness centrality $\mathcal{C}_{\rm e}^{\rm B}$ and edge eigenvector centrality $\mathcal{C}_{\rm e}^{\rm E}$.

Edge betweenness centrality (of edge $k$) can be defined as[55,56]

$$\mathcal{C}_{\rm e}^{\rm B}(k) = \frac{2}{V(V-1)} \sum_{i \neq j} \frac{q_{ij}(k)}{G_{ij}}, \qquad (3)$$

where $k \in \{1, \dots, E\}$, $\{i, j\} \in \{1, \dots, V\}$, $q_{ij}(k)$ is the number of shortest paths between vertices $i$ and $j$ running through edge $k$ and $G_{ij}$ is the total number of shortest paths between vertices $i$ and $j$. A shortest path is defined as the path between two edges for which the sum of the inverse weights of edges along this path is minimal.[30]

Edge eigenvector centrality (of edge $k$) is defined[30] as the $k$th entry of the eigenvector $\vec{v}$ corresponding to the dominant eigenvalue $\lambda_{\max}$ of matrix $\mathbf{M}$, which we derive from the eigenvector equation $\mathbf{M}\vec{v} = \lambda\vec{v}$ using the power iteration method,

$$\mathcal{C}_{\rm e}^{\rm E}(k) = \frac{1}{\lambda_{\max}} \sum_{l} M_{kl}\, \mathcal{C}_{\rm e}^{\rm E}(l), \qquad (4)$$

with $\{k, l\} \in \{1, \dots, E\}$. Here, $\mathbf{M}$ denotes the edge adjacency matrix $\tilde{\mathbf{A}}^{(\rm e)} \in \mathbb{R}_{+}^{E\times E}$ whose entries $\tilde{\mathbf{A}}_{ij}^{(\rm e)}$ are assigned the average weight of edges $i$ and $j$ if these edges are connected to a same vertex and 0 otherwise.

With the aforementioned definitions, we regard an edge with the highest centrality value as most important (rank 1) and the one with the lowest centrality value as least important (rank $E$). In the case of equal centrality values, we rank in order of appearance.

## D. Identifying important sets of edges in time-dependent interaction networks

With the aforementioned edge-centrality concepts, we employ our previously proposed edge-centrality-based network decomposition technique[30] that allows us to identify a bottom-up hierarchy of sets of edges (or "webs"), where each set is associated with a different level of importance. The decomposition technique consists of the following steps:

0. initialize algorithm: set $E' = E$ and set iteration $q = 1$;
1. estimate centrality $\mathcal{C}_{\rm e}(k)$ for all edges $k \in \{1, \dots, E'\}$ in the current network;
2. choose the lowest centrality value as threshold value $\Theta = \min_k \mathcal{C}_{\rm e}(k)$, in order to eliminate less central edges;
3. every edge $k'$ with $\mathcal{C}_{\rm e}(k') \leq \Theta$ is assigned to the web of rank $q$ and is removed from the current network (which decreases $E'$; note that the $<$ sign holds for repetitions of step 3 within the $q$th iteration);
4. repeat step 1 and step 3 until no further edge is assigned to the web of rank $q$;
5. continue with next iteration (increase $q$ by 1) at step 1, as long as there are remaining edges to be assigned to webs; and
6. reverse ranking of webs; the most important web has rank 1.

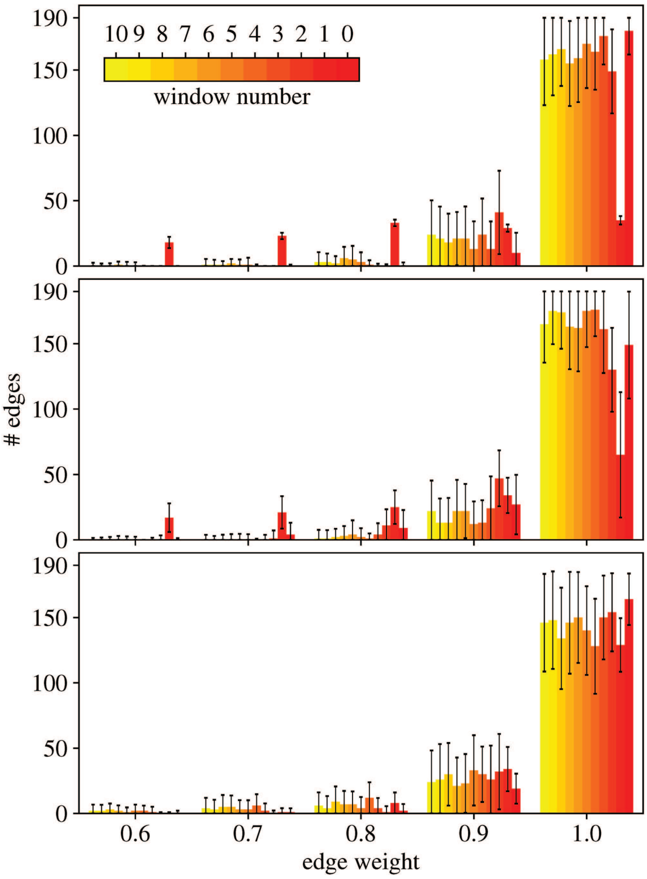

**FIG. 2.** Edge weight distributions (means and standard deviations obtained from observations of the respective amount of extreme events) of time-dependent interaction networks A, B, and C (from top to bottom) for each time window. Time window 0 is positioned around the extreme events, and the window number increases while going back in time.

We note that this network decomposition can lead to two divisions of a network that are not helpful in identifying sets of edges associated with different levels of importance. These cases are either an assignment of all edges to only one web (number of webs $N_W = 1$) or an assignment of each edge to a web ($N_W = E$). We also note that edges in a web do not have to be connected with each other.

## III. RESULTS

As shown earlier,[31,35] extreme events in the dynamics of coupled FitzHugh–Nagumo oscillators are preceded by proto-events during which a fraction of the units (those with low values of the control parameter $b$) become excited and which turn into extreme events, if and only if this fraction is sufficiently large (note that not

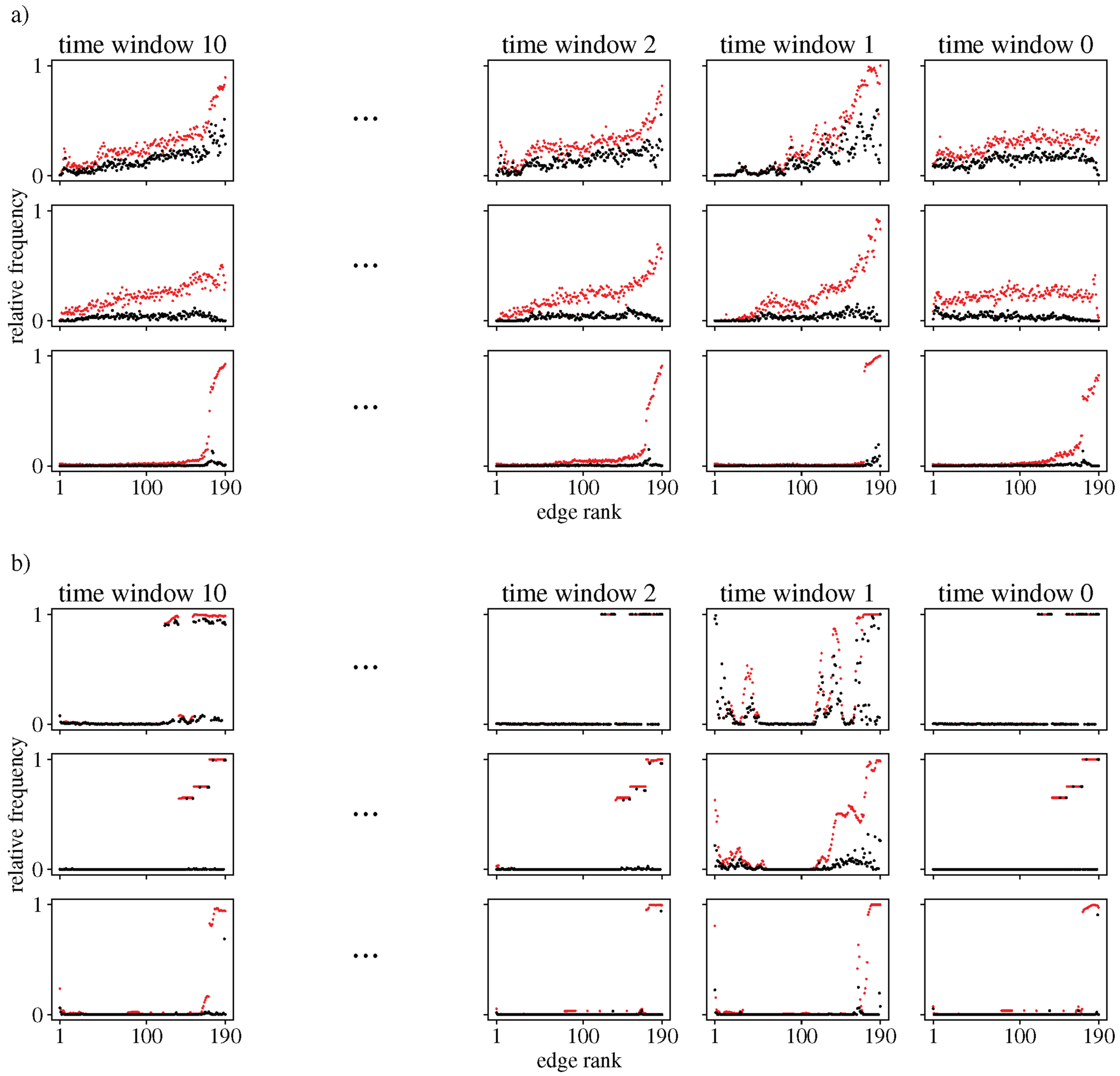

**FIG. 3.** Relative frequency of an edge with a given rank to be connected to a vertex whose dynamics exhibits proto-events. Edge rank estimated via ranking of (a) edge eigenvector centrality and (b) edge betweenness centrality. Time window 0 is positioned around the extreme events, and the window number increases while going back in time. Data from 195, 138, and 830 extreme events in the time-dependent interaction networks A, B, and C (from top to bottom). Red dots indicate edges in the time-depended interaction networks and black dots edges from the underlying coupling topology.

all proto-events are followed by an extreme event). It is, however, not yet clear how the other units are being recruited into the final generation of an extreme event. We conjecture that the recruitment is facilitated by certain edges (or sets thereof), and in the following, we will identify and characterize these edges employing the edge-centrality concepts and the edge-based network decomposition technique. Given that most of the complexity of a interaction network is encoded into the topology of interactions among its vertices (i.e., edges) and into the layout of the interactions' weights,[57–60] we first investigate how the edge weight distributions change when our time-dependent interaction networks transit into an extreme event. Since edge weights represent the strengths of interaction between units [estimated with $R_{nm}$; see Eq. (2)], we expect a narrow range of large edge weights despite the constant and rather low coupling strengths $K$. Indeed, the edge weight distribution peaks close to the maximum value of $R_{nm} = 1$ with a rather narrow spread, by construction (see Fig. 2).

For our time-dependent interaction networks, we find edge weights from the time window capturing an extreme event to compare to those from most preceding windows. Interestingly though, we observe decreased edge weights in the time window directly preceding the extreme event (window 1), and this decrease is most pronounced for networks A and B. With our analysis approach, proto-events thus reflect a desynchronized state during which only few units are simultaneously excited while the other units are not. We note that similar desynchronization phenomena were observed prior to epileptic seizures recorded in humans[61] and in a simple dynamical model of two interacting networks of integrate-and-fire neurons that mimics such an event.[62]

Since edge weights impact on the centrality concepts employed here (cf. Sec. II C) and given our previous observations, we next hypothesize that a certain amount of edges in the interaction networks from the time windows prior to the extreme event will rank among the ones with highest centrality and are, therefore, possibly more relevant for the recruitment of further units. In order to check this hypothesis, we estimate—for each time window—the probability $\mathcal{P}$ for an edge to be identified as most important (i.e., highest centrality value and thus highest rank) with the respective edge centrality. For each network, and independently of the used centrality, we observe (data not shown) in each time window (including time window 0) the respective probability distributions to peak around a small amount of edges (if we neglect edges with $\mathcal{P} < 0.2$). In addition, we observe that these distributions differ in the time window prior to the extreme event, indicating that during this time window other edges are most important.

Given these findings, we further investigate which edges are connected to vertices whose dynamics exhibit proto-events and whether these edges have a high rank and can be traced back to the underlying coupling topology (direct edge) or not (indirect edge). As shown in Fig. 3, we observe edges with low rank to be (on average) more frequently connected to such vertices in all time windows preceding time window 1. In time window 1, we additionally observe few more high-ranked edges to be frequently connected to these vertices; however, this findings holds for importance estimated using $\mathcal{C}_e^{\mathrm{B}}$ only. If importance was estimated using $\mathcal{C}_e^{\mathrm{E}}$, the low-ranked edges are even more frequently connected to these vertices. However, the underlying coupling topologies had no influence on these findings, the differences seen for the two edge centralities can be related to the differences in their conceptual basis. While $\mathcal{C}_e^{\mathrm{E}}$ considers the centrality of the neighborhood of a given edge, $\mathcal{C}_e^{\mathrm{B}}$ is a path-based approach to identify a central edge. For either centrality concept, it is rather straightforward to understand that in time windows far from the extreme event, high-ranked edges are not expected to be connected to the few vertices whose dynamics exhibit proto-events. In the time window prior to the extreme event, the opposite can be observed with $\mathcal{C}_e^{\mathrm{B}}$. This indicates that the recruitment of non-excited vertices

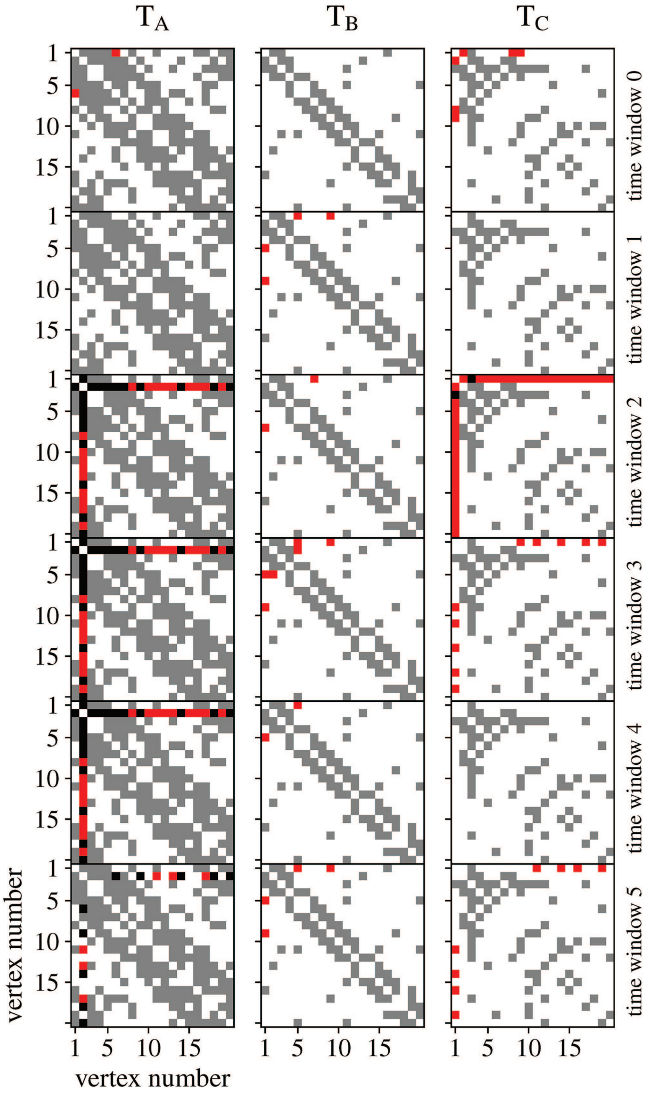

**FIG. 4.** Adjacency matrices of least important webs projected onto the underlying coupling topology (grey) with direct and indirect edges marked black and red, respectively. Only edges with a relative frequency (occurrence in data from respective amount of extreme events) higher than 75% were considered. $\mathcal{C}_e^{\mathrm{E}}$-based network decomposition. Vertices sorted in ascending order of the control parameter $b$.

is facilitated via short paths from excited vertices, making it more likely for edges that are directly connected to such vertices to have a high rank. On the other hand, with $\mathcal{C}_e^E$ highest-ranked edges connect non-excited vertices as these are mostly stronger connected (larger edge weights) non-excited vertices.

For direct edges and independent of their centrality ranking, we furthermore observe a general decrease, in time window 1 compared to other time windows, in their relative frequency to be connected to a vertex whose dynamics exhibits proto-events. One can thus deduce that most of the edges that are connected to a vertex whose dynamics exhibits a proto-event represent indirect edges with few exceptions found with betweenness centrality.

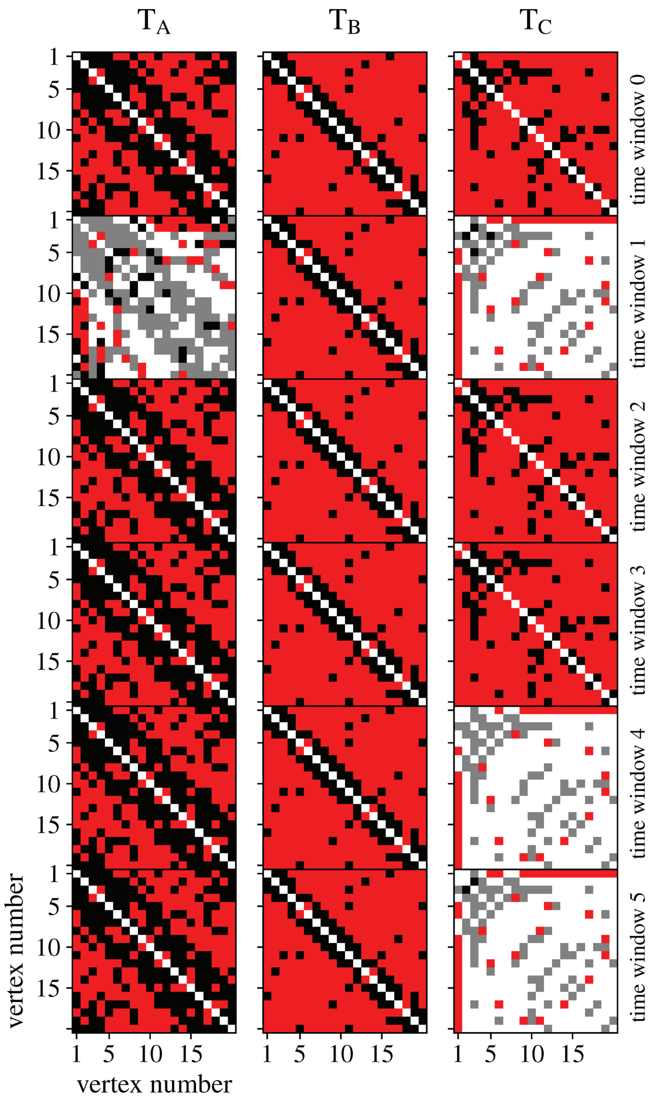

**FIG. 5.** Same as Fig. 4 but for $\mathcal{C}_e^B$-based network decomposition.

Summarizing our findings discussed so far, we conclude that the recruitment of non-excited units into the generation of an extreme event is facilitated by the most important and the least important indirect edges. As a last point, we investigate whether these edges form specific sets. To this end, we employ our edge-centrality-based network decomposition technique to identify—for each time window—the most and the least important web and eventually detail their characteristics. Our results presented in Figs. 4 and 5 indicate that the least important webs for time window 1 consist of smaller sets of edges than the ones in the least important webs identified for windows preceding window 1 or even for the window that captures the extreme event. These sets consists to a greater amount of indirect edges than of direct edges. In general, differences are most distinct for networks A and C and for the $\mathcal{C}_e^B$-based network decomposition. We note that we achieved similar findings when considering the most important webs (data not shown).

Interestingly, the sets seen for time window 1 are composed of edges (either direct or indirect ones) connected to vertices whose dynamics exhibit proto-events. As expected the $\mathcal{C}_e^B$-based decomposition mostly identifies long-range connections while the $\mathcal{C}_e^E$-based decomposition mostly identifies (nearest or next-nearest) neighboring connections within the web.

It can be summarized that distinct sets of primarily indirect edges appear to play a vital role (in the time window prior to the extreme event) for the recruitment of non-excited units into excitation leading up to an extreme event.

## IV. CONCLUSIONS

We investigated which edges in networks of coupled, excitable FitzHugh–Nagumo units facilitate the recruitment of non-excited units into the final generation of an extreme event. With an eye on typical experimental situations that explore excitable system, we investigated the importance of edges in time-dependent interaction networks. We derived these networks from investigating the strength of interaction between time series of the units' dynamics in a time-resolved manner. Importance of edges and sets thereof were characterized with the concept of edge centrality and an edge-centrality-based network decomposition technique, respectively. Our findings indicate that the recruitment of non-excited units is facilitated primarily by sets of certain most and least important edges, both of which have no equivalent in the underlying topology. A more comprehensive understanding of the role of such indirect edges and their relationship to the underlying coupling topology might aid to gain further insights into the generation of extreme events in natural networked dynamical systems.

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## DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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# Reconfiguration of human evolving large-scale epileptic brain networks prior to seizures: an evaluation with node centralities

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**Previous research has indicated that temporal changes of centrality of specific nodes in human evolving large-scale epileptic brain networks carry information predictive of impending seizures. Centrality is a fundamental network-theoretical concept that allows one to assess the role a node plays in a network. This concept allows for various interpretations, which is reflected in a number of centrality indices. Here we aim to achieve a more general understanding of local and global network reconfigurations during the pre-seizure period as indicated by changes of different node centrality indices. To this end, we investigate—in a time-resolved manner—evolving large-scale epileptic brain networks that we derived from multi-day, multi-electrode intracranial electroencephalograpic recordings from a large but inhomogeneous group of subjects with pharmacoresistant epilepsies with different anatomical origins. We estimate multiple centrality indices to assess the various roles the nodes play while the networks transit from the seizure-free to the pre-seizure period. Our findings allow us to formulate several major scenarios for the reconfiguration of an evolving epileptic brain network prior to seizures, which indicate that there is likely not a single network mechanism underlying seizure generation. Rather, local and global aspects of the pre-seizure network reconfiguration affect virtually all network constituents, from the various brain regions to the functional connections between them.**

Epilepsy is one of the most common neurological diseases globally, affecting an estimated 50 million people worldwide, and accounting for 0.5% of the global burden of disease[1]. Even in countries where adequate diagnosis and treatment are available, around 30% of epilepsies are pharmacoresistant, failing to respond to conventional medical therapy[2]. In these cases, subjects with epilepsy may be candidates for surgical intervention, which allows around 70% of these subjects to remain seizure-free for at least 1 year after surgery[3]. Among several other aspects, this failure to achieve long-lasting freedom from seizures, even after removal of the pre-surgically identified seizure onset zone (SOZ), suggests an alternative interpretation of seizure generation (ictogenesis) in epilepsy.

In recent years, epilepsy has been investigated as a network disease[4–7]. In a large-scale evolving epileptic brain network, sampled brain regions represent nodes, whereas the time-varying functional interactions between them (regardless of their anatomical connectedness) constitute the time-dependent edges of the network[8]. This results in a sequence of networks that evolve in time. When considering the SOZ as a node (or a small group of nodes) in the evolving epileptic brain network, previous studies reported the SOZ to play only a minor role in seizure dynamics[9,10], in contrast to earlier observations[11–13]. A more recent study[14] of evolving epileptic brain networks has identified nodes, whose time-dependent changes in node centrality carry predictive information about an impending seizure. More importantly, these predictive nodes were exclusively associated with brain regions far away from the SOZ, in accordance with a number of previous findings achieved with different analysis concepts[15]. This study indicated a reconfiguration of various network properties of evolving epileptic brain networks during the pre-seizure period, which is not confined to nodes related to the SOZ but extends to the whole network. A more detailed characterisation of node centrality can aid in understanding this reconfiguration and subsequently can help to shed more light on how seizures arise from epileptic brain networks. Indeed, a large number of different centrality indices have been developed to characterise the various roles the constituents play

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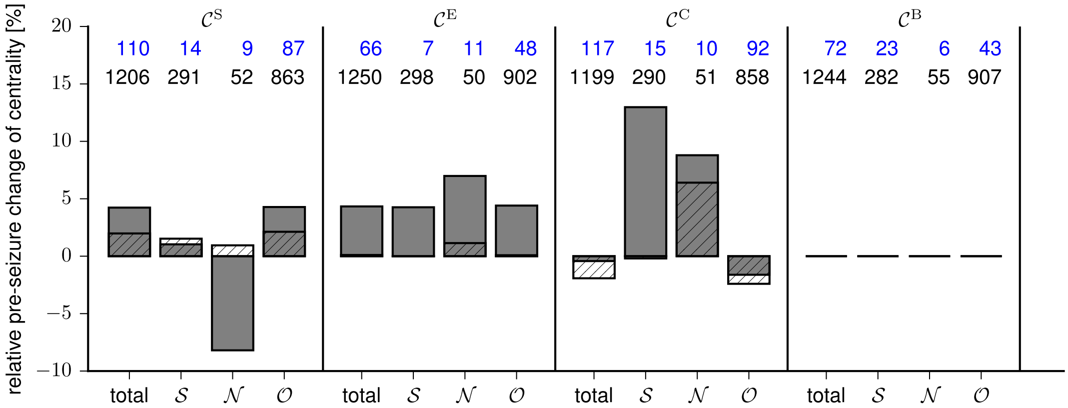

**Figure 1.** Relative pre-seizure change of centrality values of nodes in the different modules. Non-hatched/hatched bars represent median values over predictive/non-predictive nodes (median pre-seizure centrality values referenced against median centrality values from seizure-free periods). Blue/black numbers on top represent the number of predictive/non-predictive nodes in each module ($\mathcal{C}^\mathrm{S}$ strength centrality; $\mathcal{C}^\mathrm{B}$ betweenness centrality; $\mathcal{C}^\mathrm{C}$ closeness centrality; $\mathcal{C}^\mathrm{E}$ eigenvector centrality; "total" refers to the sum of these nodes). As betweenness centrality often yields values of 0, calculating a relative difference is not always possible, therefore we refer to the median absolute value which here amounts to 0.005 independent of the module (SOZ: $\mathcal{S}$, neighbours: $\mathcal{N}$, others: $\mathcal{O}$).

in the network[16–18]. Here, we consider four of the most widely used centrality indices[17], two different interaction-strength-based centrality indices (strength centrality $\mathcal{C}^\mathrm{S}$ and eigenvector centrality $\mathcal{C}^\mathrm{E}$) and two different path-based centrality indices (closeness centrality $\mathcal{C}^\mathrm{C}$ and betweenness centrality $\mathcal{C}^\mathrm{B}$). According to strength centrality, a node is central if it is strongly connected to adjacent nodes. Eigenvector centrality considers the influence of a node on the network as a whole, where a node is considered central if the nodes connected to it are also central. A node with a high closeness centrality is central as information from this node can reach all other nodes in the network via short paths, and so the node can exert a more direct influence over the network. A node with a high betweenness centrality acts as a bridge between other parts of the network. $\mathcal{C}^\mathrm{S}$ and $\mathcal{C}^\mathrm{C}$ are more sensitive to local aspects of the network, as they only consider edges immediately connected to the investigated node. On the other hand, $\mathcal{C}^\mathrm{E}$ and $\mathcal{C}^\mathrm{B}$ are more sensitive to global aspects, as they consider all edges in the network when determining the centrality of any node.

Our long-term aim is to achieve a more general understanding of how the evolving epileptic brain network changes prior to seizures and how these changes relate to the emergence of seizures from subjects with epilepsy whose seizures originated from different brain regions ("Methods" section). To this end, and in order to avoid making any assumptions about a possible influence of the underlying structural and functional aspects of the respective pathologies, we here pooled the data of the heterogeneous group of subjects with pharmacoresistant epilepsies and used multiple centrality indices. We then investigated undirected, weighted evolving epileptic brain networks which we inferred from multi-day, multi-electrode intracranial electroencephalographic recordings ("Methods" section).

## Results

Given the individualised clinical evaluation, number and anatomical locations of intracranial electrodes were highly variable between subjects ("Methods" section). For this reason, we assigned electrode contacts to functional modules (seizure onset zone (SOZ) $\mathcal{S}$, direct neighborhood of SOZ $\mathcal{N}$, and all remaining contacts (others) $\mathcal{O}$; "Methods" section)[19].

Borrowing statistical concepts from seizure prediction to identify nodes that carry predictive information of an impending seizure ("Methods" section), we find that different centrality indices ("Methods" section) generally identified different nodes as predictive, as expected. Out of 1316 total nodes, 227 (17%) were found to be predictive with at least one centrality (110 with $\mathcal{C}^\mathrm{S}$, 66 with $\mathcal{C}^\mathrm{E}$, 117 with $\mathcal{C}^\mathrm{C}$ and 72 with $\mathcal{C}^\mathrm{B}$). On the level of functional modules, each sampled brain region was frequently identified as predictive by multiple centralities, and functional module others $\mathcal{O}$ was identified most commonly even when correcting for the high variability of the electrode contacts in each functional module. This finding concurs with magnetic resonance imaging (MRI) studies in other subjects with epilepsy, which have revealed structural abnormalities outside of and even contralateral to the SOZ in multiple aetiologies of epilepsy[20–23].

We investigated how the centrality of nodes changed during the pre-seizure period. To this end, we calculated the medians of the distributions of centrality values from the pre-seizure and the seizure-free period (for each node and centrality index respectively). We used the relative difference between the distributions' median values to determine whether centrality values, on average, increased or decreased prior to seizures. As summarised in Fig. 1, we generally observed an increase of centrality values prior to seizures, except in the case of $\mathcal{C}^\mathrm{S}$ for nodes in the functional module neighbours $\mathcal{N}$ and $\mathcal{C}^\mathrm{C}$ for nodes in the functional module others $\mathcal{O}$. For nodes that were not predictive, we generally observed a less pronounced, but qualitatively comparable change than for predictive nodes (except for nodes in module $\mathcal{N}$ when using $\mathcal{C}^\mathrm{S}$).

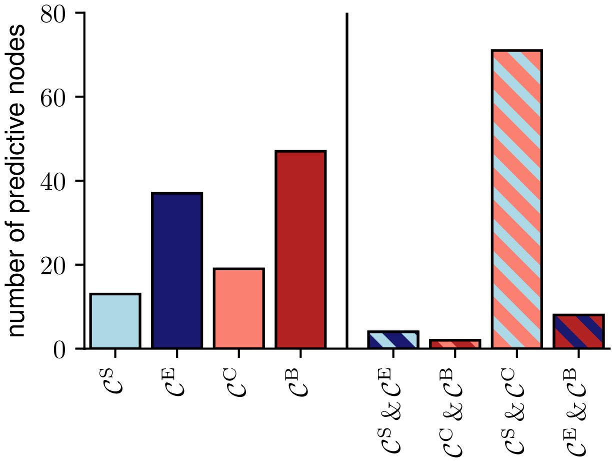

**Figure 2.** Predictive nodes as identified with only respective centralities or combinations of such. For example, there are 13 nodes identified as predictive with $\mathcal{C}^{\mathrm{S}}$, that are not identified as predictive with the other three centralities, and 4 nodes identified as predictive with $\mathcal{C}^{\mathrm{S}}$ and $\mathcal{C}^{\mathrm{E}}$, that are not identified as predictive with the other two centralities. Different colours indicate different centralities (light blue: strength centrality $\mathcal{C}^{\mathrm{S}}$; dark blue: eigenvector centrality $\mathcal{C}^{\mathrm{E}}$; light red: closeness centrality $\mathcal{C}^{\mathrm{C}}$; dark red: betweenness centrality $\mathcal{C}^{\mathrm{B}}$). Centrality indices considering local/global aspects of the evolving epileptic brain network are depicted in light/dark colour respectively, while strength-/path-based centrality indices are depicted in blue/red. Hatched bars indicate a combination of the respective centralities (see colours above).

With the aforementioned predictive changes in centrality values, we next investigated whether the observed increase is associated with a re-ordering of node importance within the epileptic brain network. To determine the relative importance of predictive nodes, they were ranked by average centrality value (for each centrality separately, for seizure-free and pre-seizure periods respectively). Interestingly, predictive nodes were neither the most nor the least important ones but ranked among the top of the lower half. Moreover there was no significant difference between average rank of these nodes from pre-seizure and seizure-free periods for any centrality individually. This may indicate that pre-seizure changes are not necessarily confined to specific brain regions, but rather that there is, on average, an increase in interaction strength between all nodes in the epileptic brain network prior to seizures, consistent with findings in previous studies[14,19].

Subsequently, we investigated whether different centrality indices identify the same nodes as predictive. While we find that a majority of nodes are identified as predictive with only one centrality index, unexpectedly, a substantial number of nodes were identified as predictive with two or more indices (see Fig. 2). To further investigate the information gain from using multiple centrality indices, we separated the 227 predictive nodes into groups according to the centrality index or indices with which they were identified as predictive. Betweenness centrality and eigenvector centrality each identified the largest number of nodes as predictive (47 and 37 nodes, respectively) followed by closeness centrality (19 nodes) and strength centrality (13 nodes). It is to be noted that even two centrality indices based on the same network-theoretical concept (interaction-strength- or path-based), rarely identified the same predictive nodes. On the other hand, the largest group of nodes identified as predictive were congruently found with strength centrality and closeness centrality (a total of 71 nodes). Of note, this is a combination of two different network-theoretical concepts, which both consider local network characteristics. More rarely were nodes identified as predictive with combinations of three or all four centralities, which indicates that typically only some and not all aspects of the evolving epileptic brain network change during the pre-seizure period.

Given these findings, we propose several major scenarios for a pre-seizure reconfiguration of the evolving epileptic brain network, that can be inferred from significant differences between node centralities from the pre-seizure and seizure-free periods in the various functional modules (Fig. 3). In the following, we concentrate on the five most common occurrences of predictive nodes as identified with only respective centralities or combinations of such.

**Scenario 1** (based on observations with strength centrality $\mathcal{C}^{\mathrm{S}}$; Fig. 3a): As already described in a previous study[14], during the pre-seizure period a small number of nodes both related to the seizure onset zone (SOZ) and brain regions far off the SOZ, become more strongly connected to the other nodes of the evolving epileptic brain network. Meanwhile, nodes related to the neighbourhood of the SOZ become less connected. Since we employed a synchronisation-based measure (mean phase coherence) to estimate the strength of interactions, this could indicate a loss of synchronisation, i.e., a decoupling of the neighbourhood from the rest of the network, while the latter interacts more strongly locally. A pre-seizure decrease in synchronisation has been hypothesised to be a state of increased susceptibility for pathological synchronisation during a seizure[24] or depression of synaptic inhibition[25], possibly allowing an easier transition to seizure activity. These findings could lead to the assumption that path structures traversing these nodes in the evolving epileptic brain network change prior to seizures. Surprisingly, however, as not all of these nodes carry predictive information

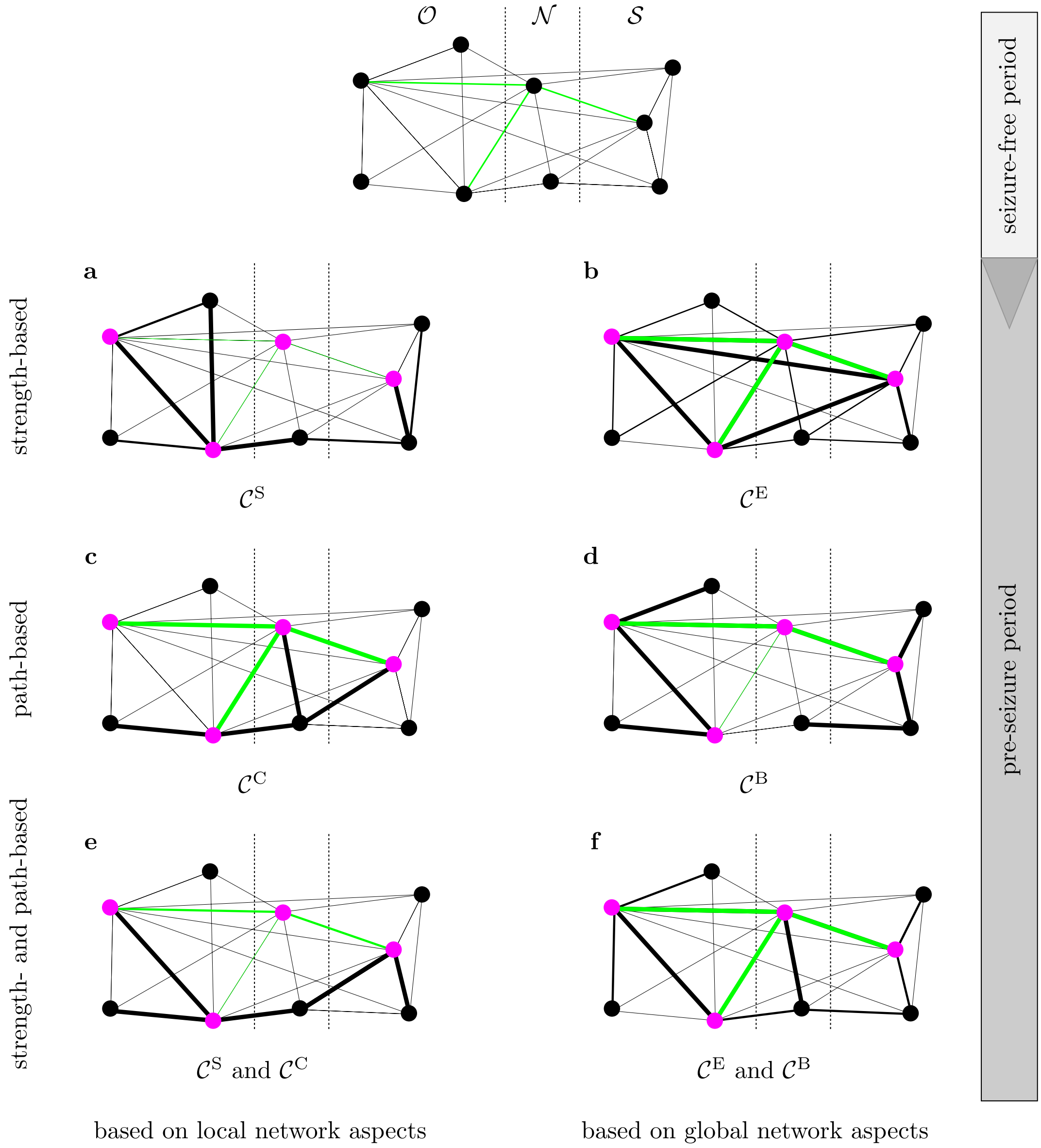

**Figure 3.** Scenarios for the pre-seizure reconfiguration of the evolving epileptic brain network. Schematic of the network divided into the three functional modules (others $\mathcal{O}$, neighbours $\mathcal{N}$, SOZ $\mathcal{S}$; separated by dashed lines). The different sub-figures (**a**–**f**) represent how the network during the seizure-free period (top) would change prior to seizures if the pink nodes were deemed predictive with the respective local and global interaction-strength-based and path-based centrality indices or combinations thereof (note that different centrality indices generally identified different nodes as predictive; we here restrict ourselves to just a few nodes to simplify visualisation). The networks can be assumed to be fully connected, however, for the purpose of visualisation, edges that remain unchanged during seizure-free and pre-seizure periods are not shown. Shortest paths identified in the seizure-free period (examples) are marked green. The thickness of an edge represents its edge weight: the thicker an edge the shorter the path traversing the edge or the stronger the connection between nodes. ($\mathcal{C}^{\mathrm{S}}$: strength centrality; $\mathcal{C}^{\mathrm{E}}$ eigenvector centrality; $\mathcal{C}^{\mathrm{C}}$ closeness centrality; $\mathcal{C}^{\mathrm{B}}$: betweenness centrality).

(when assessed with closeness centrality $\mathcal{C}^{\mathrm{C}}$ and betweenness centrality $\mathcal{C}^{\mathrm{B}}$), path structures traversing these nodes remain unchanged. This indicates that the general exchange of information between brain regions remains largely unaffected during the pre-seizure period, which might explain the rare occurrence of epileptic prodromes[26,27].

**Scenario 2** (based on observations with eigenvector centrality $\mathcal{C}^{\mathrm{E}}$; Fig. 3b): Beyond the local scope of strength centrality, our results obtained with the more global eigenvector centrality indicate that strongly connected nodes are strongly connected especially to each other prior to seizures, highlighting hub-like structures[28]. This is, however, not necessarily a formation of new hub-like structures, since their connection strength to the rest of the epileptic brain network does not change prior to seizures, as indicated by the lack of a significant change in their strength centrality. This is also supported by the fact that path structures traversing the hub-like structures remain unchanged. Moreover, since hub-like structures are not confined to any particular brain region (as also found in a structural study[29]), this might point to a recruitment of even brain regions assumed to be unaffected by the pathology, hereby contributing to the generation of seizure activity.

**Scenario 3** (based on observations with closeness centrality $\mathcal{C}^{\mathrm{C}}$; Fig. 3c): The shortening of the paths seen between nodes related to the SOZ and to its neighbourhood, as well as to the rest of the epileptic brain network prior to seizures, indicates that information can flow more easily along the paths connecting these network constituents. This is not necessarily accompanied by a profound increase in coupling between constituents (as indicated by $\mathcal{C}^{\mathrm{S}}$) nor by a higher number of shortest paths traversing these nodes (as indicated by $\mathcal{C}^{\mathrm{B}}$). However, as we can not infer the direction of this information flow with the methods applied here, several potential ictogenic mechanisms can be considered: e.g. nodes related to the SOZ recruit other nodes in the larger network into the generation of seizures[30,31]. This recruitment might also be facilitated by the fact that information flow between nodes far off the SOZ and its neighbourhood becomes less effective during the pre-seizure period (lengthening of the shortest paths). In contrast, nodes related to brain regions deemed unaffected by the pathology might recruit nodes related to the SOZ and/or its neighbourhood into the generation of seizures. Whatever the exact mechanism might be, these possibilities underline that the generation of seizures in any one part of the epileptic brain network is influenced by activity everywhere else in the network[4].

**Scenario 4** (based on observations with betweenness centrality $\mathcal{C}^{\mathrm{B}}$; Fig. 3d): Expanding the previous interpretation[14] of the formation of bottlenecks during the pre-seizure period, the unexpected lack of congruence between findings obtained with $\mathcal{C}^{\mathrm{C}}$ and $\mathcal{C}^{\mathrm{B}}$ (both centrality indices would identify the same node as relevant for the flow of information through the epileptic brain network) points to a general decrease in information flow (increased length of shortest paths), except through those nodes that become bottlenecks. On the one hand, this would indicate that the formation of bottlenecks can be regarded as an epiphenomenon, while on the other hand and since we here observed bottlenecks almost in the whole network these nodes possibly form a backbone of the evolving epileptic brain network.

**Scenario 5** (based on observations with strength centrality $\mathcal{C}^{\mathrm{S}}$ and closeness centrality $\mathcal{C}^{\mathrm{C}}$; Fig. 3e): If we combine the information about pre-seizure changes in the epileptic brain network gained with local (and to a lesser extent also with global; Fig. 3f) path- and interaction-strength-based centrality indices, our findings point to groups of nodes associated with the SOZ and with brain regions far off the SOZ becoming more strongly connected prior to seizures, while the connection between these groups weakens and information flow within the whole network becomes hampered. This indicates a compartmentalisation of brain regions, which has been hypothesised to cause an increased vulnerability to the spreading of seizure activity[32]. Similar compartmentalisation has also been observed during seizures[33,34]. We speculate that the compartmentalisation seen before and during seizures results from the same underlying process.

## Conclusion

While previous studies already showed that the temporal change of node centrality—possibly induced by a reconfiguration of properties of evolving epileptic brain networks—can carry predictive information about impending seizures, we here aimed at a more comprehensive perspective of this reconfiguration. These networks—evolving, large-scale, fully connected networks (spanning lobes and hemispheres)—were constructed from iEEG data, with nodes representing the sampled brain regions and edges the time-varying functional interactions between them. By considering four different centrality indices (local and global interaction-strength-based and path-based indices), that reflect changes in the evolving epileptic brain network differently, and by using established statistical methods to identify nodes that carry predictive information[35], we can now trace these changes which are specific to the pre-seizure period.

Pre-seizure changes in the network are not necessarily confined to specific brain regions, but rather there is, on average, a pre-seizure increase in interaction strength between all nodes in the epileptic brain network, consistent with findings in previous studies[14,19]. Moreover, with our proposed scenarios, we conclude that there is likely not a single network mechanism underlying ictogenesis. Rather, they point to local and global reconfigurations of the evolving large-scale epileptic brain network affecting virtually all network constituents, from the various brain regions to the (functional) connections between them.

An important limitation in this retrospective study was the high variability in implantation schemes for electrodes, which were purely clinically driven and relate to the structural and functional heterogeneity of the underlying disease. In many subjects with epilepsy, the area around the suspected SOZ is usually spatially oversampled, while data from other brain regions are often very limited or even absent. Even in subjects with greater electrode coverage, it is possible that evolving epileptic brain networks were incomplete as not all brain regions were sampled[15]. It is therefore possible that there are important regions for ictogenesis which lie outside of those considered in this study. Among others, there were several possible confounding influences on the distinction between dynamics from seizure-free and pre-seizure periods: subjects were often sleep-deprived and all had their individual antiepileptic medication dose tapered as part of the pre-surgical assessment. Furthermore, the possible impact of multi-day rhythms[36–38] was not controlled for in this study, as data from multiple days were pooled for each subject.

Future studies should investigate the duration of the presumed pre-seizure period as a possible confounder. It is conceivable that there is a high inter-individual variation in pre-seizure period duration, which the variation in prodromal symptom onset and duration seems to support[39]. Finally, the results of this study should be combined with those of similar studies focusing on edges rather than nodes[19], which could be expanded to include novel edge centrality indices[40]. Previous studies have assessed whether predictive edges connect predictive nodes[14], reporting that this occurs in a majority of cases. A combination of information gained from predictive nodes and edges and their relation to the underlying anatomy and physiology could provide a more complete understanding

| Subj. | Age | Sex | Dur | MRI | Loc | Out | Szr | $D_{\mathrm{tot}}$ | $D_{\mathrm{int}}$ | $D_{\mathrm{pre}}$ | $N$ | $N_{\mathcal{S}}$ | $N_{\mathcal{N}}$ | $N_{\mathcal{O}}$ | $\#\mathcal{C}_{\mathrm{pred}}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 54 | Male | 46 | R AHS | RMT | 2B | 1 | 228 | 224 | 4 | 86 | 3 | 2 | 81 | 0 |
| 2 | 34 | Male | 29 | L FCD | LF | 1A | 7 | 111 | 85 | 26 | 26 | 5 | 5 | 16 | 4 |
| 3 | 15 | Female | 10 | R AHS | LT,RT |  | 4 | 162 | 146 | 16 | 66 | 44 | 0 | 22 | 0 |
| 4 | 45 | Female | 42 | L AHS | LT | 1A | 1 | 146 | 142 | 4 | 48 | 12 | 2 | 34 | 0 |
| 5 | 25 | Female | 21 | w.p.f. | RMT | 1A | 1 | 82 | 78 | 4 | 58 | 10 | 1 | 47 | 0 |
| 6 | 22 | Male | 23 | w.p.f. | RMT | 1A | 5 | 94 | 74 | 20 | 74 | 10 | 1 | 63 | 0 |
| 7 | 57 | Male | 51 | Hamartia | RFPo | 1A | 3 | 71 | 61 | 10 | 72 | 14 | 11 | 47 | 3 |
| 8 | 39 | Female | 11 | R AHS | RT | 1A | 3 | 91 | 79 | 12 | 52 | 11 | 3 | 38 | 0 |
| 9 | 24 | Female | 23 | AHS bilat. | LMT,RMT |  | 2 | 20 | 14 | 6 | 42 | 20 | 0 | 22 | 1 |
| 10 | 34 | Male | 33 | L AHS, L FCD | LMT | 1A | 4 | 70 | 54 | 16 | 52 | 20 | 4 | 28 | 0 |
| 11 | 25 | Male | 24 | L AHS | LMT | 1A | 3 | 26 | 17 | 9 | 58 | 3 | 5 | 50 | 0 |
| 12 | 43 | Female | 27 | w.p.f. | LT | 1A | 3 | 94 | 85 | 9 | 56 | 8 | 0 | 48 | 4 |
| 13 | 29 | Male | 17 | L AHS | LMT,RMT |  | 4 | 92 | 76 | 16 | 120 | 20 | 4 | 96 | 1 |
| 14 | 38 | Male | 15 | AHS bilat. | LMT | 1A | 2 | 52 | 44 | 8 | 46 | 8 | 4 | 34 | 0 |
| 15 | 44 | Female | 31 | L FCD | LF | 1A | 1 | 103 | 99 | 4 | 14 | 4 | 0 | 10 | 0 |
| 16 | 52 | Male | 52 | L AHS | LMT | 1A | 1 | 49 | 45 | 4 | 42 | 5 | 4 | 33 | 3 |
| 17 | 45 | Male | 24 | w.p.f. | LT,RT |  | 3 | 116 | 107 | 9 | 72 | 28 | 0 | 44 | 2 |
| 18 | 31 | Female | 14 | w.p.f. | RT | 1A | 2 | 74 | 69 | 5 | 36 | 11 | 1 | 24 | 3 |
| 19 | 25 | Female | 6 | w.p.f. | LMT,RMT |  | 5 | 161 | 142 | 19 | 90 | 8 | 1 | 81 | 4 |
| 20 | 53 | Female | 13 | L AHS | LP | 1A | 1 | 46 | 42 | 4 | 24 | 11 | 3 | 10 | 0 |
| 21 | 62 | Female | 50 | Dysplasia | RFPa |  | 3 | 94 | 84 | 10 | 56 | 39 | 1 | 16 | 2 |
| 22 | 44 | Female | 30 | L AHS | LT,RT | 1A | 3 | 129 | 117 | 12 | 46 | 30 | 0 | 16 | 2 |
| 23 | 25 | Male | 13 | R FCD | RFP | 1A | 3 | 18 | 8 | 10 | 30 | 5 | 4 | 21 | 2 |
| 24 | 26 | Female | 10 | Dysplasia | LT | 1A | 1 | 26 | 22 | 4 | 16 | 5 | 4 | 7 | 1 |
| 25 | 54 | Female | 49 | R FCD | RT | 1A | 1 | 67 | 63 | 4 | 62 | 9 | 7 | 46 | 0 |
| 26 | 27 | Female | 16 | w.p.f. | LMT | 1A | 2 | 163 | 155 | 8 | 48 | 10 | 2 | 36 | 4 |
| 27 | 28 | Female | 25 | R AHS | LMT,RMT |  | 2 | 126 | 121 | 5 | 46 | 21 | 1 | 24 | 0 |
| 28 | 19 | Male | 9 | AHS bilat. | LFT,RFT |  | 2 | 47 | 40 | 7 | 78 | 34 | 2 | 42 | 2 |
| 29 | 26 | Female | 18 | w.p.f. | LMT | 2A | 3 | 97 | 85 | 12 | 36 | 10 | 0 | 26 | 1 |
| 30 | 37 | Male | 5 | R AHS | RMT | 1A | 2 | 103 | 95 | 8 | 46 | 10 | 4 | 32 | 4 |
| 31 | 25 | Male | 26 | L AHS | LFT,RFT |  | 2 | 32 | 25 | 7 | 78 | 0 | 0 | 78 | 0 |
| 32 | 37 | Male | 2 | w.p.f. | LMT | 1A | 4 | 68 | 52 | 16 | 65 | 6 | 0 | 59 | 2 |
| 33 | 15 | Female | 11 | L FCD | LFPo | 1A | 2 | 36 | 28 | 8 | 30 | 8 | 7 | 15 | 1 |
| 34 | 24 | Male | 4 | w.p.f. | LMT | 1A | 2 | 67 | 59 | 8 | 65 | 6 | 3 | 56 | 4 |
| 35 | 22 | Male | 18 | Lesion | LFT | 1A | 3 | 19 | 7 | 12 | 38 | 4 | 2 | 32 | 2 |
| 36 | 29 | Female | 12 | w.p.f. | LMT,RMT |  | 2 | 37 | 29 | 8 | 88 | 6 | 1 | 81 | 3 |
| 37 | 41 | Female | 13 | w.p.f. | LMT,RM |  | 2 | 127 | 119 | 8 | 118 | 13 | 5 | 100 | 4 |
| 38 | 27 | Female | 13 | L FCD | LSMA | 1A | 2 | 67 | 59 | 8 | 30 | 6 | 7 | 17 | 0 |

**Table 1.** Subject demographics. *Age* age at time of presurgical evaluation, *Dur* duration of epilepsy in years, *MRI* MRI findings (*w.p.f.* without pathological findings, *AHS* Ammon's horn sclerosis, *bilat.* bilateral, *FCD* focal cortical dysplasia), *L* left, *R* right, *Loc* location of seizure onset zone (*MT* mesial temporal, *SMA* supplementary motor area, *P* parietal, *F* frontal, *Fpo* frontopolar, *Fpa* frontoparietal, *FT* frontotemporal, *T* temporal), *Out* epilepsy surgery outcome scale [48] (no surgery performed if empty entry), *Szr* number of clinical seizures; $D_{tot}$ total recording duration in hours, $D_{int}$ total duration of seizure-free periods in hours, $D_{pre}$ total duration of pre-seizure periods in hours; $N$ total number of electrode contacts, $N_{\mathcal{S}}$ number of electrode contacts in functional module "SOZ"; $N_{\mathcal{N}}$ number of electrode contacts in functional module "neighbours", $N_{\mathcal{O}}$ number of electrode contacts in functional module "others", $\#\mathcal{C}_{\mathrm{pred}}$ number of centralities that identified predictive nodes.

of ictogenesis in evolving epileptic brain networks, could help to identify better targets for future treatment strategies[41–43], and could support the translation of the network approach into clinical practice.

## Methods

**Data.** In this retrospective study, we analysed multi-day, multi-electrode intracranial EEG (iEEG) recordings from 38 subjects with pharmacoresistant epilepsies with different anatomical origins (Table 1). The data were part of previous studies[8,14,19]. Between 2002 and 2012, 380 subjects with drug-resistant epilepsy underwent presurgical evaluation with intracranial electroencephalographic recordings. From this sample, we included subjects for which either a single or multiple seizure onset zones (SOZ) had been identified and resected, as well as subjects with multiple, non-resectable SOZs. We only included data from subjects if they had at least 18 h of recording that captured at least one seizure (with or without secondary generalisation). Recordings spanned an average of 83 h (total: 3239, range 18–228), and captured 2.5 clinical seizures on average (total: 99, range 1–7). Subclinical seizures were neglected in our analyses. Placement and number of electrodes were decided for each subject individually, and were entirely clinically driven (average number of contacts: $N = 56$, range 16–120). The study was approved by the ethics committee of the University of Bonn, and all subjects with epilepsy had signed informed consent that their data could be used and published for research purposes. A parent or legal guardian gave written informed consent on behalf of the participant if below the age of 18. All experiments were performed in accordance with relevant guidelines and regulations.

For cortical surface recordings, subdural strip electrodes (four or eight platinum contacts with an intercontact distance of 10 mm) and/or subdural grid electrodes ($8 \times 4$ or $8 \times 8$ platinum contacts with an intercontact distance of 10 mm) were used. These types of electrodes were implanted in 74% of subjects. For recordings from the mesial temporal lobes, depth electrodes (equipped with 10 or 8 cylindrical contacts of nickel–chromium alloy; length: 2.5 mm, intercontact distance: 4 mm) were implanted using either a trans-occipital (10-contact electrodes) or orthogonal-to-the-mesial-structures approach (8-contact electrodes) to the hippocampus[44]. In five subjects, 8-contact depth electrodes were also implanted into lesions or focal cortical dysplasias. iEEG data were sampled at 200 Hz using a 16 bit analogue-to-digital converter, band-pass filtered between 0 and 45 Hz (4th order Butterworth characteristic), and a notch filter was used to suppress the power line frequency (50 Hz). Recorded signals were referenced against the average of two contacts which were selected for each subject individually, located distant from the suspected seizure onset zone (SOZ).

Seizures were identified by board-certified epileptologists on the iEEG and concomitant video recording. We divided data into pre-seizure and seizure-free periods. Recordings within the 4 h preceding an electrophysiologically defined seizure event were classified as pre-seizure[45]. Recordings within the 30 min after seizure onset were excluded from this analysis in order to not bias our analyses with effects from the seizure and particularly from the post-ictal period[46,47]. All remaining recording data were considered to be from the seizure-free period. Following pre-surgical analysis, board-certified epileptologists identified at least one SOZ in all subjects, being the region where electrical seizure activity was first identified. The electrode contacts within this SOZ were labelled as $\mathcal{S}$ for subsequent analyses. Electrode contacts not more than two contacts distant to the SOZ ("neighbours" or $\mathcal{N}$) were also considered separately to other electrode contacts more distant to the SOZ ("others" or $\mathcal{O}$). These classifications are subsequently referred to as "functional modules"[19].

Subjects received different antiepileptic drugs (AEDs) with different mechanisms of action, and the majority of subjects were under combination therapy with two or more AEDs. During presurgical evaluation AEDs were reduced in a subject-specific manner, and many subjects did not have discontinuation of all AEDs.

### Identifying evolving epileptic brain networks.

Following previous studies (e.g.[14,19,45]), we used a sliding window approach and estimated the strength of time-varying functional interactions between brain regions $n$ and $m$ ($(n, m) = 1, \dots, N$) sampled by the implanted electrodes, using mean phase coherence[49]:

$$R_{nm} = \left| \frac{1}{T} \sum_{j=0}^{T-1} e^{i(\Phi_n(j) - \Phi_m(j))} \right|.$$

$T$ is the number of data points per window and $\Phi_n$ is the instantaneous phase time series of node $n$ that we derived from the Hilbert transform of the iEEG time series of node $n$. An important property of this analytic signal approach (particularly in case of two or more superimposed oscillatory components) is that the instantaneous frequency relates to the predominant frequency in the Fourier spectrum[50,51]. Since the predominant frequency may be subject to fluctuations in the iEEG time series, the instantaneous frequency can vary rhythmically around the predominant frequency resulting in spurious estimates of the instantaneous phase. Such effects can nevertheless be reduced, e.g., by taking the temporal average. Note that from an electrophysiological point of view, it might be more reasonable to look adaptively (e.g., via the Hilbert transform) at interactions between predominant rhythms in the iEEG than to look at interactions in some a priori fixed frequency bands (e.g., via wavelet) for which there is no power in the time series[51,52]. $R_{nm}$ falls within the range [0, 1], where $R_{nm} = 1$ indicates fully phase-synchronised brain regions, while $R_{nm} = 0$ indicates no phase synchronisation.

A non-overlapping sliding-window with $T = 4096$ data points (20.48 s duration) was used to calculate $R_{nm}$ for all possible combinations of brain regions (nodes $(n, m)$). Mean phase coherence values were used as edge weights in subsequent network analysis, while electrode contacts represented nodes, resulting in a sequence of undirected, weighted and fully connected epileptic brain networks.

### Estimating node centrality indices.

For each node in the evolving epileptic brain network , we calculated four different centralities: strength centrality ($\mathcal{C}^{\mathrm{S}}$; which is equivalent to degree centrality in unweighted networks[53,54]), eigenvector centrality ($\mathcal{C}^{\mathrm{E}}$), closeness centrality ($\mathcal{C}^{\mathrm{C}}$), and betweenness centrality ($\mathcal{C}^{\mathrm{B}}$). This calculation was repeated for each time-window, in order to assess changes in a node's centrality over time.

According to strength centrality, a node is central if it is strongly connected to adjacent nodes, and is defined as the summed weights of edges connected to the node:

$$\mathcal{C}^{\mathrm{S}}(n) = \sum_{m=1}^{N} R_{nm},$$

where $R_{nm}$ is the weight of the edges connecting nodes $n$ and $m$, and nodes $n$ and $m$ are adjacent.

Eigenvector centrality considers the influence of a node on the network as a whole, where a node is considered central if the nodes connected to it are also central, and is defined as

$$\mathcal{C}^{\mathrm{E}}(n) = \frac{1}{\lambda_{\max}} \sum_{m=1}^{N} R_{nm}\, \mathcal{C}^{\mathrm{E}}(m),$$

where $\lambda_{\max}$ is the dominant eigenvalue of the weighted adjacency matrix, $R_{nm}$ is the weight of edges between nodes $n$ and $m$, and $\mathcal{C}^{\mathrm{E}}(m)$ is the eigenvector centrality of node $m$. This equation is applied iteratively until eigenvector centrality values remain stable.

Closeness centrality considers the distance between a node and all other nodes in the network. A node with a high closeness centrality is central as information from this node can reach all other nodes in the network via short paths, and so the node can exert a more direct influence over the network. $\mathcal{C}^{\mathrm{C}}$ is calculated as follows:

$$\mathcal{C}^{\mathrm{C}}(n) = \frac{1}{\sum_{m=1}^{N} d_{nm}},$$

where $d_{nm}$ is the length of the shortest path between nodes $n$ and $m$, calculated as the sum of the inverse of all edge weights on the path.

Finally, betweenness centrality is a measure of how frequently a given node falls on the shortest path between two other nodes. A node with a high betweenness centrality is central because it acts as a bridge between other brain regions. Betweenness centrality of a node $n$ is given by

$$\mathcal{C}^{\mathrm{B}}(n) = \frac{2}{(N-1)(N-2)} \sum_{l \neq m \neq n} \frac{q_{lm}(n)}{G_{lm}},$$

where $G_{lm}$ is the number of shortest paths between nodes $l$ and $m$, and $q_{lm}(n)$ is the number of shortest paths between nodes $l$ and $m$ which pass through node $n$. The length of a path is calculated as the sum of the inverse of all edge weights on that path.

Both $\mathcal{C}^{\mathrm{C}}$ and $\mathcal{C}^{\mathrm{B}}$ consider shortest paths in some sense. A path between two nodes describes a series of edges (which can be just one edge) that are traversed when going from one node to the other. A path is considered short or strong (long or weak) if the sum of the inverse edge weights along this path is small (large). Accordingly, we employed two different interaction-strength-based centrality indices ($\mathcal{C}^{\mathrm{S}}$ and $\mathcal{C}^{\mathrm{E}}$) and two different path-based centrality indices ($\mathcal{C}^{\mathrm{C}}$ and $\mathcal{C}^{\mathrm{B}}$). While eigenvector centrality was iteratively calculated for all nodes in the network, and thus takes into account more global aspects of the network, strength centrality only considers the strength of interactions of a given node to its adjacent ones, reflecting only local aspects of the network. In case of betweenness centrality, the global path structure in the network is considered (by identifying all shortest paths) when estimating the centrality of a node, while for closeness centrality only local path structures are considered, namely the shortest paths from the node, for which the centrality is estimated, to every other node in the network. Hence, $\mathcal{C}^{\mathrm{S}}$ and $\mathcal{C}^{\mathrm{C}}$ are more sensitive to local aspects of the network compared to $\mathcal{C}^{\mathrm{E}}$ and $\mathcal{C}^{\mathrm{B}}$. Note that the term local does not refer to a spatial relationship, as we estimated the centralities for fully connected networks, but to certain edges that are either directly connected to the node for which the centrality is calculated, or are a part of a shortest path connected to this node. $\mathcal{C}^{\mathrm{E}}$ and $\mathcal{C}^{\mathrm{B}}$ are sensitive to global aspects, as they consider all edges in the network, when determining the centrality of any node.

### A statistical approach to identify predictive nodes.

In order to determine whether a node's centrality changed prior to a seizure, we compared its distributions of values from pre-seizure and seizure-free periods using the Kolmogorov–Smirnov (KS) test. The $p$-values of this test were corrected for multiple comparisons (number of nodes) using the Bonferroni method. In order to be considered for further analysis, a node's centrality had to significantly differ between pre-seizure and seizure-free periods ($p < 0.05$).

In order to verify the specificity of this change, and to minimise the impact of confounding variables such as the influence of rhythmic fluctuations in interaction strength[8], seizure time surrogates (STS) were created to compare the real data to[55]. 19 STS time-lines were created for each subject, where "seizure times" were placed randomly within the seizure-free periods, but maintained the same total number of seizures and the distribution of intervals between sequential seizures. The KS test was then repeated for each of these STS datasets. If the test revealed larger KS-statistic values (the largest distance between two cumulative distributions) when comparing centrality values of pre-seizure to seizure-free periods for the STS than for the real data, then any difference found in the real data could be explainable by changes of node centrality due to unrelated fluctuations in network topology, e.g. measurement errors or daily rhythms. Using this method we determined the number of predictive nodes. In order to be identified as predictive, a node's KS-statistic value had to be at least 5% greater (to compensate for estimation errors) than any of its KS-statistic values for STS for at least one centrality (note that the KS-statistic is not sensitive to the direction of change). Given the different sizes (number of electrode contacts, Table 1) of functional modules within subjects, the hypergeometric statistic was used to test whether more nodes located within one module were predictive than expected by chance ($p < 0.05$).

With any of the employed centrality indices, we identified at least one predictive node in 23 of 38 subjects with epilepsy (Table 1), and only data from these subjects will be considered in subsequent analyses. Statistical analysis found no significant correlation between the identification of predictive nodes and the subjects' age, sex, duration of epilepsy, surgery outcome, location of the SOZ (hemisphere and lobe), or number of electrodes. We note that our findings are neither dominated by data from a single nor from few specific subjects.

## Data availibility

The data that support the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available as they contain information that could compromise the privacy of research participants.

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## Author contributions

All authors designed the study, analysed the data and wrote the manuscript. All authors reviewed the manuscript.

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The authors declare no competing interests.

## Additional information

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# Emergence of a tipping subnetwork during a critical transition in networked systems: A new avenue to extreme events

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Unexpected and often irreversible shifts in the state or the dynamics of a complex system often accumulate in extreme events with likely disastrous impact on the system and its environment. Detection, understanding, and possible prediction of such critical transitions are thus of paramount importance across a variety of scientific fields. The rather modest improvement achieved so far may be due previous research mostly concentrating on either particular subsystems, considered to be of vital importance for the generating mechanism of a critical transition, or on the system as a whole. These approaches only rarely take into account the intricate, time-dependent interrelatedness of subsystems that can essentially determine emerging behaviors underlying critical transitions. We uncover subsystems, network vertices, and the interrelatedness of certain subsystems, network edges, as tipping elements in a networked dynamical system, forming a time-evolving tipping subnetwork. We demonstrate the existence of tipping subnetworks in excitable complex networks and in human epileptic brains. These systems can repeatedly undergo critical transitions that result in extreme events. Our findings reveal that tipping subnetworks encapsulate key properties of mechanisms involved in critical transitions.

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## I. INTRODUCTION

Critical transitions are crucial phenomena in the dynamics of complex systems, where already a small change in internal or external conditions can lead to a seemingly abrupt and often irreversible shift in the systems' states. Such transitions are widely observed in different natural and man-made systems across diverse scientific fields, including ecology, economics, climate science, epidemiology, medicine, and physics [1–11]. Adopting the network perspective [12,13] and assuming these systems are composed of coupled units, representing subsystems, allows us to improve understanding of emergent phenomena, where the collective system dynamics cannot be trivially inferred from properties and dynamics of its individual units. Rather, for such emergent phenomena, complex and largely unexpected global behaviors arise from the nontrivial, local interactions together with the intricate global interplay of the systems' coupled units.

Emergent phenomena, such as critical transitions, entail possibly far-reaching and irreversible impacts and massive restrictions for the system, as they can culminate in extreme events. These are generally understood as rare yet (re)occurring large deviations from an otherwise regular system dynamics, often imposing potentially disastrous consequences on a system's stability, functionality, and overall health [14,15]. Therefore, identifying alterations of the systems' dynamics, associated with a critical transition that lead to an extreme event is of paramount importance. This would allow for predicting these events, which would enable development of effective mitigation and prevention strategies [16–19].

Advances in mathematical concepts to improve understanding of the described phenomena [20,21] as well as advances in time-series analysis techniques for data-driven detection of critical transitions and prediction of extreme events [22], however, are still unsatisfactory and at times even controversially discussed. The high dimensionality as well as the intricate interplay between structure and dynamics of real-world systems, together with stochastic influences, complicate the identification of critical transitions, prediction of extreme events, as well as the study of mechanisms that are involved in their generation. Furthermore, in many approaches, emphasis is either placed on the state of individual units or on global properties of the system. This often leads to a heuristic derivation of single and specific elements, so-called tipping elements [23], which may shift abruptly and irreversibly from one state to another. However, in many complex systems, and not least because of their emergent properties, all interactions, i.e., the ways in which coupled units influence each other, play a central role not only in determining the systems' dynamics, but also for transitions between different dynamics [24–26]. The description of complex systems as networked systems of coupled units emphasizes the relevance of interactions.

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In many natural and man-made complex systems, however, access to couplings is limited or even impossible. The aforementioned description of a system as a network is still possible when considering network vertices as units and network edges as interactions between them, constituting a functional network. This requires characterizing interactions from time series of appropriate observables of the units' dynamics, together with the choice of an estimator for the strength and/or direction of an interaction or even for the coupling function, depending on the specific research question and the system under investigation.

Here, we go beyond the recently proposed relevance of interacting tipping elements, or networks thereof, that has been put forward particularly for the Earth's climate system [27–31]. We argue that significant advances in understanding critical transitions in the dynamics of networked systems can be achieved by shifting the focus from either a global perspective or from a unit-centric view to one that emphasizes the identification of temporal and structural patterns of interactions between units, but on an intermediate level between single constituents and the entire network. We define these constituents, vertices and edges, as tipping vertices and tipping edges that exhibit significant alterations in their structural integration within the functional interaction network prior to an extreme event. We conjecture that a tipping subnetwork, a connected network consisting of tipping vertices and tipping edges, together with its integration within the larger networked system can provide vital insights into critical transitions and network alterations associated with their generation.

Here, we demonstrate the presence of a tipping subnetwork in toy models of excitable complex networks as well as in a complex natural system, the human epileptic brain. For these systems some knowledge about the mechanisms associated with critical transitions is available, as they relate to complex phase synchronization phenomena [32,33], and systems are capable of self-generating and self-terminating extreme events, i.e., without changing control parameters. Eventually, we highlight the exceptional integration and seclusion of the tipping subnetwork in the larger time-evolving network.

## II. INVESTIGATED SYSTEMS

### A. Excitable complex networks

We model excitable complex networks locally by the FitzHugh-Nagumo equation [34,35], a paradigmatic model for excitability with broad applicability in diverse fields such as neuron dynamics, cardiac physiology, cell division, population dynamics, and electronics [36–39]. Following Ref. [40], our networks consist of $V = 101$ diffusively coupled FitzHugh-Nagumo oscillators, where the dynamics of the $i$th oscillator is governed by

$$\begin{aligned}\dot{x}_i &= x_i(a - x_i)(x_i - 1) - y_i + k\sum_{j=1}^{V} A_{ij}(x_j - x_i)\\ \dot{y}_i &= b_i x_i - c y_i.\end{aligned} \tag{1}$$

The oscillator's control parameters are $a$, $b_i$, and $c$, and $\mathbf{A} \in \{0, 1\}^{V\times V}$ is the adjacency matrix of a nondirectional network, in which each vertex corresponds to one FitzHugh-Nagumo oscillator: $A_{ij} = A_{ji} = 1$, if oscillators $i$ and $j$ are coupled. We disregard any self-coupling (loops): $A_{ii} = 0\ \forall i \in [1, V]$.

Following previous studies [32,40–43], we consider paradigmatic networks (small-world (SW) [44], scale-free (SF) [45], and random (RN) [46]) as coupling topologies, and additionally consider an all-to-all coupling (complete network; CP) to cover situations encountered in investigations of empirical data.

We choose the global coupling strength $k$ such that the collective network dynamics (ensemble average of the excitatory dynamical variable $x$) exhibits extreme events ($k = 18.1820$ for a small-world network with $E = 202$ edges and rewiring probability $p = 0.25$; $k = 4.9458$ for a scale-free network with $E = 198$ and $m = 3$ initial vertices; $k = 4.2065$ for a random network with $E = 258$; $k = 0.128$ for complete network with $E = 5050$). These extreme events are self-generated and self-terminated [32,40–43] and manifest as rare, short-lived, and large-amplitude events, which strongly deviate from an otherwise normal oscillatory dynamical behavior (average value of first dynamical variable exceeds four standard deviations of normal oscillatory behavior; Fig. 1). We observe 10–30 of such events in the time series of the collective network dynamics for each of the 20 realizations of each coupling topology.

### B. Human epileptic brain

Epilepsy is among the most common diseases of the brain and affects approximately $50 \times 10^6$ people worldwide [47]. The disease is mainly characterized by the repeated occurrence of epileptic seizures, an abnormal and excessively synchronized neuronal activity that temporarily and often massively disrupts normal brain function [48]. Epilepsy is now viewed as a network disorder with seizures emerging from large-scale brain networks [49]. Although access to the brain's coupling topology is limited, important information about an epileptic brain network's dynamics can nevertheless be achieved from investigating time-evolving functional networks [(TEFNs), Sec. III A] derived from electroencephalographic recordings (Fig. 2). In this framework, a TEFN's vertices are associated with sampled brain regions, and its edges represent properties of time-dependent interactions between the region's dynamics [50], yielding a time-evolving complete network. We investigate multiday electroencephalographic (EEG) recordings encompassing 123 seizures from 48 individuals with epilepsy (refer to Appendix A for detailed information).

## III. METHODS

### A. From multivariate time series to time-evolving functional networks

A functional (or interaction) network can be derived from multivariate time series of a system's dynamics as follows [51,52]: associate subsystems (respectively, sensors that record the subsystems' dynamics) with network vertices ($v_m \in \mathcal{V}$, $m \in \{1, \dots, V\}$, $V = |\mathcal{V}|$) and associate properties

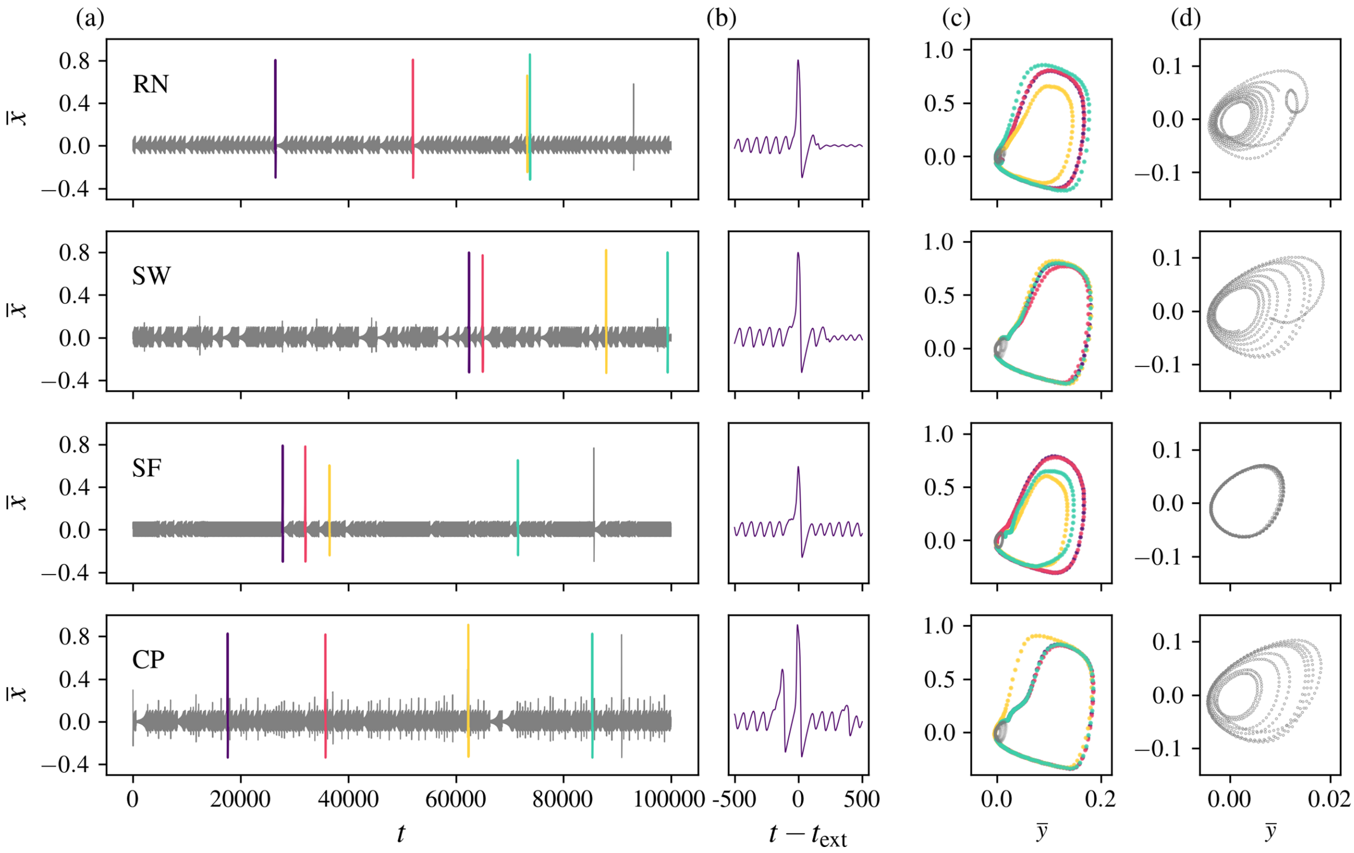

FIG. 1. Dynamics of excitable complex networks [coupling topologies: random (RN); small-world (SW); scale-free (SF); all-to-all (complete; CP)]. (a) Exemplary temporal evolutions of the average value of the first dynamical variable $\bar{x} = \frac{1}{V}\sum_{i=1}^{V} x_i$ [Eq. (1)] exhibiting extreme events. (b) Excerpts centered around an extreme event (at $t_{\text{ext}}$, where $\bar{x} \geqslant 4\sigma_x$; $\sigma_x$ denotes the standard deviation of $\bar{x}$) of the respective time series. Note that the excitable complex networks are also capable of generating clusters of extreme events consisting of closely following events that are not preceded by the normal oscillatory dynamics. For our investigations, we only consider the first event of a cluster. (c) Attractor projection on the $(\bar{y}, \bar{x})$ plane of extreme event dynamics [colors refer to extreme events in (a)]. (d) Attractor projection on the $(\bar{y}, \bar{x})$ plane of the normal (oscillatory) dynamics. The control parameters $a = -0.02651$ and $c = 0.02$ are identical for all oscillators; the parameter $b_i = 0.006 + 0.008\frac{i-1}{V-1}$ is mismatched with $0.006 \leqslant b_i \leqslant 0.014\, \forall i$ [40]. Each networks' dynamics was integrated using an adaptive, explicit Runge-Kutta method of fifth order with a step size of 1 [53]. We chose initial conditions randomly near the attractor and discarded at least $10^3$ initial transients. Time series (here: $x$ components) used for further analyses consisted of $10^5$ data points.

of an interaction between each pair of subsystems with network edges ($e_i \in \mathcal{E}, i \in \{1, \dots, E\}, E = |\mathcal{E}|$, with $e_i = e_{mn} = \{v_m, v_n\}$ and $v_m \in \mathcal{V},\ v_n \in \mathcal{V}$). Properties of an interaction include existence (binary network), strength (weighted network), or direction (directed network) and can be estimated with bivariate time-series analysis techniques [54–57]. For a time-resolved analysis of the system's dynamics, as in the case of a nonstationary system [22,58], the multivariate time series can be split into consecutive windows (e.g., during which the system can be assumed to be approximately stationary; Fig 3). This then results in a time-dependent sequence of functional snapshot networks [a time-evolving functional network (TEFN); Fig. 3] whose number of vertices and edges remains constant but the strength of the pairwise interactions between vertices (represented by the weight of the edges) varies.

Since generating mechanisms of critical transitions observed in the systems investigated here relate to synchronization phenomena [43,59–64], we employ a measure for phase synchronization to estimate the strengths of pairwise interactions. The mean phase coherence between the time series of vertices $v_m$ and $v_n$ is defined as [65]

$$R_{mn} = \left| \frac{1}{T} \sum_{t=0}^{T-1} e^{i(\phi_{v_m}(t) - \phi_{v_n}(t))} \right|, \tag{2}$$

where $T$ denotes the number of data points per window and $\phi_{v_m}$ is the time series of instantaneous phase of the dynamics of vertex $v_m$, which we derived using the Hilbert transform. $R_{mn}$ is confined to the unit interval with $R_{mn} = 1$ indicating fully phase-synchronized subsystems. Mean phase coherence values between time series from all pairs $(v_m, v_n)$ ; $(m \neq n)$ of vertices define the weighted adjacency matrix $\mathcal{W}^{V \times V}$, whose diagonal elements are set to zero to avoid self-loops. This matrix describes an undirected, weighted functional snapshot network (Fig. 3).

For the multivariate time series of the excitable complex networks, we choose $T$ such that each sliding window contains at least one full cycle of either an extreme event or a low-amplitude oscillation (Fig. 3). This resulted in around 1000 snapshot networks for each realization of an excitable complex network.

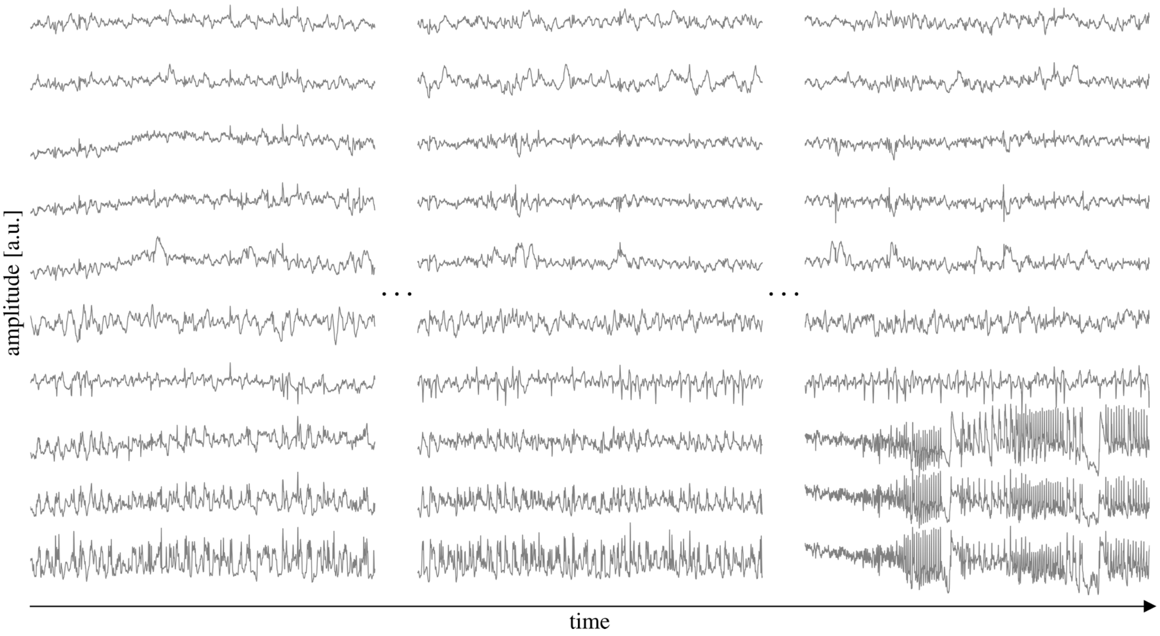

FIG. 2. Exemplary electroencephalographic recordings from a subject with epilepsy (Appendix A). Excerpts of 30 s duration from different brain regions (top to bottom) during times far off seizure-related dynamics (left), during the critical transition (middle), and at onset of a focal seizure (right).

For the multivariate time series of epileptic brain dynamics, we choose $T$ to cover a window of 20 s duration, which represents a compromise between the required statistical accuracy for the calculation of $R_{mn}$ and approximate stationarity within a window length [58]. This resulted in, on average, 20300 snapshot networks for the investigated epileptic brain networks (range: 2300–48000; Appendix A).

### B. Identifying tipping elements in time-evolving functional networks

We define tipping elements as those network constituents whose alterations of their structural integration (assessed with centralities; Appendix B) during critical transitions to recurrent extreme events differ significantly from alterations seen far from critical transitions. In case of the human epileptic brain, we also consider short-term fluctuations to minimize the influence of biological rhythms that act on various time scales [66]. We identify tipping elements by adopting an analysis approach that is successfully applied in studies on the detection of precursors of epileptic seizures [49,59,67].

To this end, we first assume a critical transition to take a certain amount of time that covers the generation of an extreme event (critical transition period $\mathrm{P}_{\mathrm{crit}}$ with duration $T_{\mathrm{crit}}$). We also assume that the period starting a certain amount of time after the previous extreme event and ending with the onset of the next critical transition does not cover the generation, dynamics, and possible enduring effects of an extreme event (period of normal dynamics $\mathrm{P}_{\mathrm{norm}}$ with duration $T_{\mathrm{norm}}$).

Next, we determine whether the (fluctuations of the) structural integration [$\mathcal{C}(z)$] of network constituent $z$ differs between $\mathrm{P}_{\mathrm{crit}}$ and $\mathrm{P}_{\mathrm{norm}}$ [Fig. 3(c1)]. For this purpose, we perform a nonparametric comparison of the cumulative distribution functions (CDFs) of the respective time series of centrality values during $\mathrm{P}_{\mathrm{crit}}$ and $\mathrm{P}_{\mathrm{norm}}$ [two-sample Kolmogorov-Smirnov (KS) test, Fig. 3(c2)]. Network constituents for which we achieve a significant difference ($p < 0.05$ after Bonferroni correction to account for multiple comparisons in the order of the number of vertices/edges) serve as candidates for tipping elements. Eventually, and in order to minimize the risk of potential confounder-mediated false attributions of network constituents to tipping elements (e.g., due to fluctuations in network topology, measurement errors, etc.), we adopt a surrogate technique [22,69] that consists of a random shuffling of $\mathrm{P}_{\mathrm{norm}}$ to generate a surrogate sequence of artificial onset times of $\mathrm{P}_{\mathrm{crit}}$. We repeat the aforementioned statistical comparison for each network constituent with 19 surrogate sequences and use the maximum distance $S$ between two CDFs to judge false attributions. We identify a network constituent as tipping element only if the $S$ value of the original sequence exceeds by at least 5% the maximum $S$ value obtained from the surrogate sequences, for any of the employed centrality concepts (i.e., $\mathcal{C}^{\mathrm{S/N}} \vee \mathcal{C}^{\mathrm{E}} \vee \mathcal{C}^{\mathrm{C}} \vee \mathcal{C}^{\mathrm{B}}$).

For the dynamics of the excitable complex networks, we omit $\pm 1T$ around the extreme event and choose $T_{\mathrm{crit}} = 3T$ to capture protoevents that precede the extreme events [40–42]. We assign the remaining data to $\mathrm{P}_{\mathrm{norm}}$.

Since opinions differ on how long before a seizure the mechanisms leading to it actually begin, any recordings within 4 h prior to seizure onset were excluded from $\mathrm{P}_{\mathrm{norm}}$ and instead considered as potentially related to the $\mathrm{P}_{\mathrm{crit}}$. We hence choose $T_{\mathrm{crit}} = 4\,\mathrm{h}$ [68]. To avoid possible effects resulting from the seizure and the postseizure period, which are known to be associated with EEG alterations, recordings within 30 min after the onset of a seizure, with the onset identified by a board-certified epileptologists on the EEG and concomitant video recordings, were omitted from the analysis.

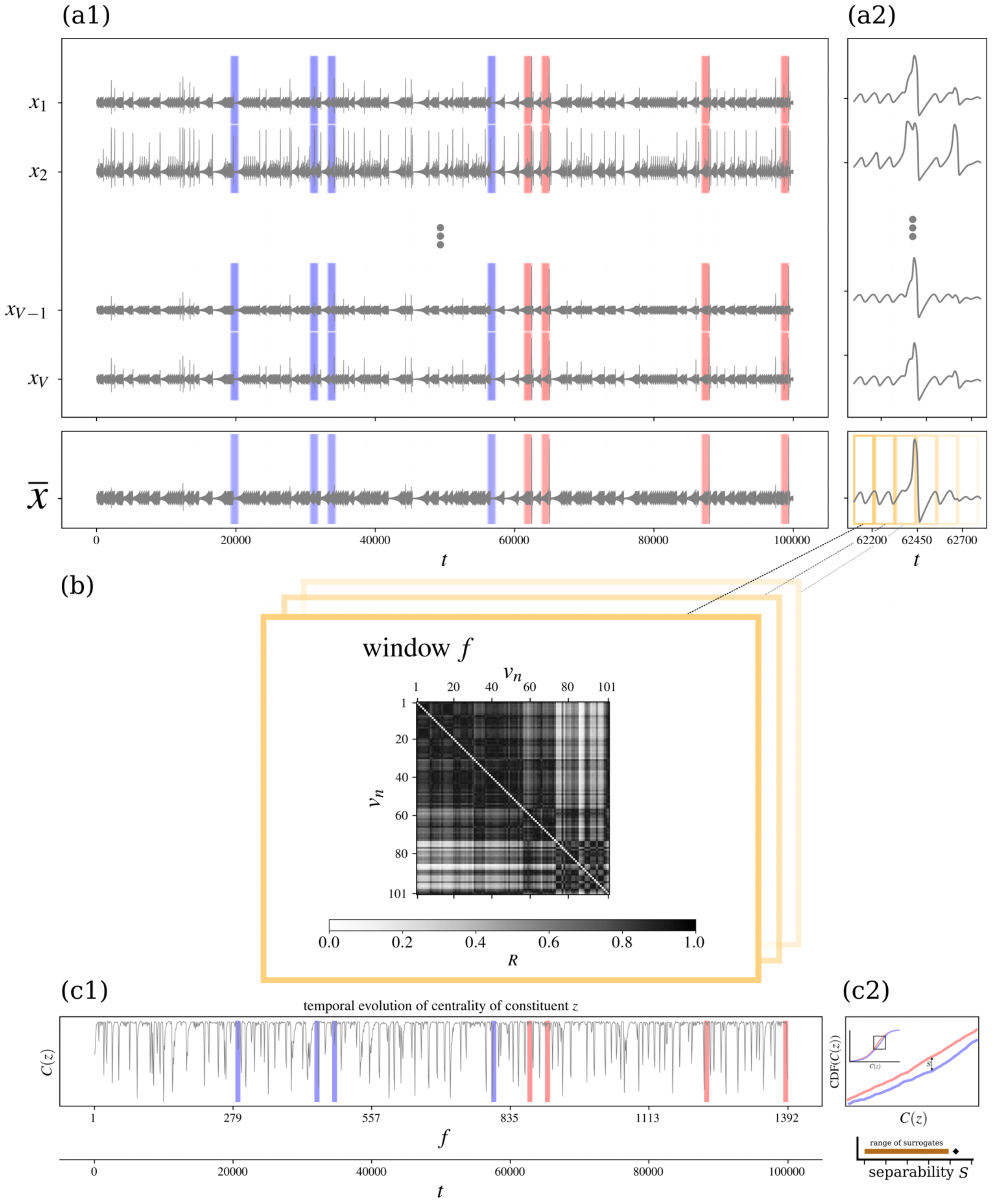

FIG. 3. Schematic representation of the methodological framework to derive time-evolving functional networks from multivariate time series of a system's dynamics and to identify tipping constituents. (a1) Exemplary time-series with marked critical transitions into extreme event (red) and surrogate extreme events (blue) [69]. (a2) Highlighted arbitrary extreme event and schematic of the sliding-window approach with nonoverlapping windows (orange). (b) Construction of time-evolving functional networks, where adjacency matrices encapsulate the strength of interactions between units as assessed with mean phase coherence $R$. (c1) Temporal evolution of a selected centrality measure of constituent $z$ with significant differences in periods associated with a critical transitions compared to normal dynamics. (c2) Exemplary cumulative distribution functions (CDF) of centrality values. Maximum separability $S$ of distributions (Kolmogorov-Smirnov statistic) is shown as double-headed arrow. The left inset shows the full CDF. The lower inset shows separability $S$ of distributions (diamond) to clearly exceed the range of $S$ values (brown bar) derived from surrogates.

## IV. RESULTS

### A. Tipping subnetworks in excitable complex networks

Extreme events in excitable complex networks are preceded by short-lived events that are characterized by only a few oscillators being excited (i.e., the corresponding $x_i$ assumes a high value) [32,40–43]. Such protoevents appear to lead to an extreme event only if excited oscillators can recruit a critical amount of other oscillators, which then also start to exhibit protoevents. Nevertheless, since extreme events were observed less frequently than protoevents, the formation of protoevents may not be regarded as the sole generating mechanism for a critical transition to an extreme event in the dynamics of excitable complex networks.

The recruitment of nonexcited oscillators is largely facilitated by sets of specific edges in the network [43]. These

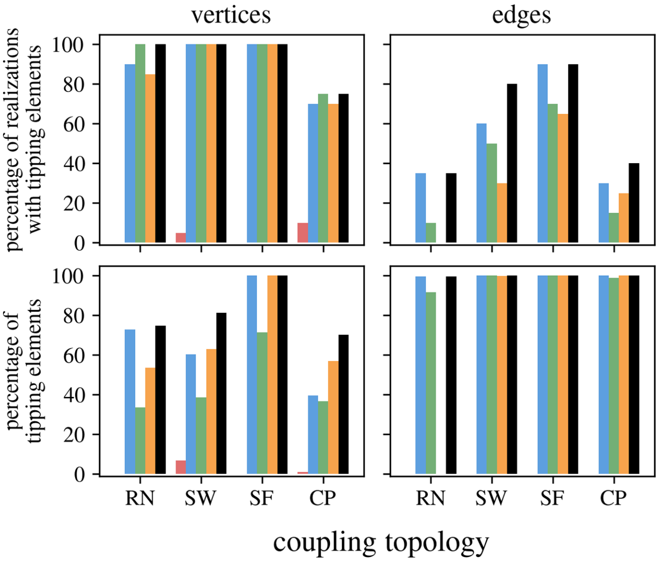

FIG. 4. Top: Percentage of time-evolving functional networks, stemming from excitable complex networks with different coupling topologies (cf. Fig. 1), with the structural integration of tipping elements (vertices or edges) quantified with different centrality concepts (color coded). Bottom: Relative amount of tipping elements in time-evolving functional networks for which any vertices or any edges were identified as tipping elements. Centrality concepts (Appendix B): $\mathcal{C}^{\mathrm{B}}$ (red); $\mathcal{C}^{\mathrm{C}}$ (blue); $\mathcal{C}^{\mathrm{E}}$ (green); $\mathcal{C}_{\mathrm{v}}^{\mathrm{S}}/\mathcal{C}_{\mathrm{e}}^{\mathrm{N}}$ (orange); with any of the concepts (black), including any constituent that has been deemed a tipping element based on either one or possibly multiple centrality measures.

edges are deemed most or least important, on average over time, based on different centrality concepts, however have no equivalent in the underlying topology. Further these edges lie not only between vertices that show protoevents but also between vertices that dot not show excitation. We argue that the formation of protoevents is governed by dynamic interactions between both excited and nonexcited oscillators in the network. These interactions are associated with distinct time-dependent alterations that underlie a critical transition to an extreme event.

We identify these alterations, or tipping subnetworks, in time-evolving functional networks [(TEFNs) that we derive from time series of the excitatory dynamical variable $x$ in Eq. (1); Sec. III A] by first quantifying how each single network constituent (oscillator or vertex, interaction or edge) is structurally integrated in the TEFNs (Appendix B) and then by segregating those constituents that qualify as precursors (or tipping elements) for an upcoming extreme event (Sec. III B) in contrast to the residual subnetwork consisting of the nontipping elements (henceforth referred to as nontipping subnetwork).

*Occurrence of tipping constituents.* We find tipping elements, vertices and edges, in all TEFNs that stem from excitable complex networks with small-world, scale-free, or all-to-all coupling topologies (SW-/SF-/CP-based TEFNs), and in two-thirds of the TEFNs stemming from excitable complex networks with a random coupling topology (RN-based TEFNs) (Fig. 4, top). In contrast to what one would expect from observations of protoevents, the amount of tipping elements is surprisingly large (Fig. 4, bottom): on average, between 70% and 80% of vertices are tipping vertices and all edges are tipping edges if we consider cases with at least one tipping edge. Of these tipping vertices, 98% are connected, on average, to a tipping edge, and between 63% and 92% of tipping edges connect two tipping vertices (data not shown). Notably, only 1%–5% of tipping edges are connected to only one nontipping vertex. Together, these findings indicate the presence of a connected, substantial tipping subnetwork within the TEFN that takes on a peculiar and pivotal role during the critical transition to an extreme event in excitable complex networks. We observe though a strong influence of the coupling topology of the excitable complex networks the TEFNs stem from: in SW- (SF)-based TEFNS, we identify a tipping subnetwork in about 75% (90%) of cases; in RN- or CP-based TEFNS, this is reduced to about one-third of cases.

Let us now examine in greater detail the changes in the structural integration (as assessed with different centralities) of the tipping subnetwork, both during critical transitions and during periods of normal dynamics. Figure 5 provides a comprehensive overview of median changes.

*Structural integration assessed with strength-based centralities.* For RN- and SW-based TEFNs, vertex strength centrality ($\mathcal{C}_{\mathrm{v}}^{\mathrm{S}}$) is slightly higher in the tipping subnetwork than in the nontipping subnetwork during normal dynamics but decreases to comparable levels during the critical transition. In SF-based TEFNs, $\mathcal{C}_{\mathrm{v}}^{\mathrm{S}}$ values drop significantly in both subnetworks during the transition. Conversely, in CP-based TEFNs, $\mathcal{C}_{\mathrm{v}}^{\mathrm{S}}$ increases slightly across the entire network.

Nearest-neighbor edge centrality ($\mathcal{C}_{\mathrm{e}}^{\mathrm{N}}$) follows a similar trend: in RN-, SW-, and SF-based TEFNs, $\mathcal{C}_{\mathrm{e}}^{\mathrm{N}}$ values decrease and converge between subnetworks during the transition, while in CP-based TEFNs, $\mathcal{C}_{\mathrm{e}}^{\mathrm{N}}$ increases in the tipping subnetwork and decreases in the nontipping subnetwork. This suggests that CP-based TEFNs develop distinct structural alterations during transitions, whereas RN-, SW-, and SF-based TEFNs become more homogenized.

Vertex and edge eigenvector centrality ($\mathcal{C}_{\mathrm{v}}^{\mathrm{E}}$, $\mathcal{C}_{\mathrm{e}}^{\mathrm{E}}$) are higher in the tipping subnetwork than in the nontipping subnetwork for RN-, SW-, and SF-based TEFNs, with the differences becoming on average more pronounced during critical transitions. While this may seem contrary to the homogenization observed in $\mathcal{C}_{\mathrm{v}}^{\mathrm{S}}$ and $\mathcal{C}_{\mathrm{e}}^{\mathrm{N}}$, higher $\mathcal{C}_{\mathrm{v}}^{\mathrm{E}}$ values indicate stronger interconnectedness between the tipping and the nontipping subnetwork. Thus, eigenvector centrality changes further support the interpretation of TEFN homogenization based on strength centrality.

*Structural integration assessed with path-based centralities.* Neither with vertex nor with edge betweenness centralities ($\mathcal{C}_{\mathrm{v}}^{\mathrm{B}}$, $\mathcal{C}_{\mathrm{e}}^{\mathrm{B}}$) do we observe significant differences between the tipping and nontipping subnetworks, and not between the normal dynamics and the critical transition. In contrast, vertex and edge closeness centralities ($\mathcal{C}_{\mathrm{v}}^{\mathrm{C}}$, $\mathcal{C}_{\mathrm{e}}^{\mathrm{C}}$) reveal differences that are qualitatively similar to those observed with strength-based centralities ($\mathcal{C}_{\mathrm{v}}^{\mathrm{S}}$ and $\mathcal{C}_{\mathrm{e}}^{\mathrm{N}}$). This is consistent with the more homogenized structures of RN-, SW-, and SF-based TEFNs, especially during the critical transitions, and the tipping subnetwork emerging as a distinct structure in CP-based TEFNs.

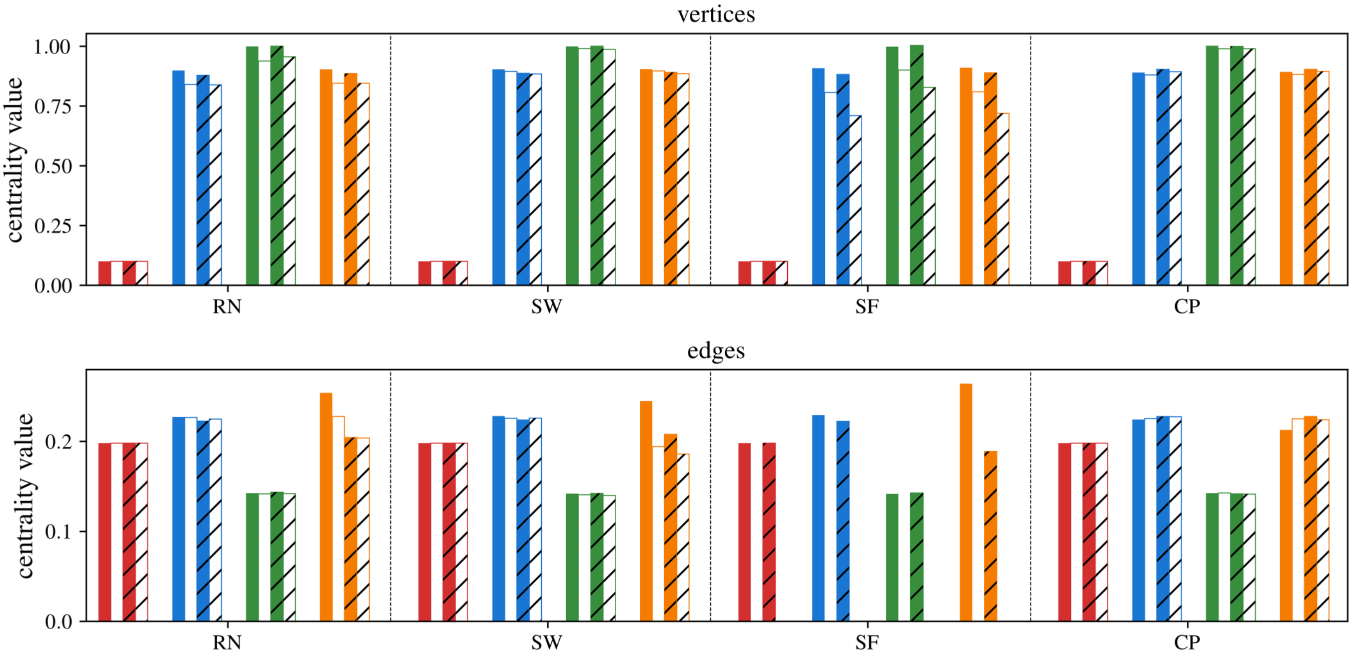

FIG. 5. Median centrality values of tipping (filled bars) and nontipping (empty bars) vertices and edges comprising subnetworks in time-evolving functional networks (TEFNs) during periods of normal dynamics (nonhatched) and during critical transitions (hatched). Median over all realizations calculated from the median centrality values of the respective vertices and edges. TEFNs were derived from excitable complex networks with a random (RN), small-world (SW), scale-free (SF), or all-to-all (CP) coupling topology. Centrality concepts (Appendix B) are color coded: betweenness $\mathcal{C}^{\mathrm{B}}$ (red); closeness $\mathcal{C}^{\mathrm{C}}$ (blue); eigenvector $\mathcal{C}^{\mathrm{E}}$ (green); strength/nearest neighbor $\mathcal{C}_{\mathrm{v}}^{\mathrm{S}}/\mathcal{C}_{\mathrm{e}}^{\mathrm{N}}$ (orange). We rescaled centrality values for easier legibility of the figure [scaling factors for vertex centralities: $(\mathcal{C}^{\mathrm{B}}, \mathcal{C}^{\mathrm{C}}, \mathcal{C}^{\mathrm{E}}, \mathcal{C}_{\mathrm{v}}^{\mathrm{S}}) = (1, 10, 100, 0.01)$; scaling factors for edge centralities: $(\mathcal{C}^{\mathrm{B}}, \mathcal{C}^{\mathrm{C}}, \mathcal{C}^{\mathrm{E}}, \mathcal{C}_{\mathrm{e}}^{\mathrm{N}}) = (1000, 10, 0.01, 0.05)$].

*Topological and spectral characteristics of the time-evolving functional network.* In addition to characteristics of single constituents (vertices and edges), global characteristics of TEFNs can provide important information on critical-transition-related network modifications [70]. We therefore calculate, for each snapshot functional network, the average shortest path length $L$, the global clustering coefficient $C$, assortativity $A$, and synchronizability $S$ (see Ref. [52] for details).

The distributions of global characteristics of the TEFNs for different excitable complex networks during normal dynamics and critical transitions are summarized in Fig. 6. For RN-, SW-, and SF-based TEFNs, the average path length ($L$) tends to be higher, while the clustering coefficient ($C$) is lower during critical transitions. Combined with a slight increase in assortativity ($A$), this suggests a breakdown of specific structures (such as clusters and path structures) and a homogenization of the TEFNs during the critical transition. The stability of the globally synchronized state, assessed with synchronizability ($S$), remains largely unchanged for RN- and SW-based TEFNs, but increases for SF-based TEFNs during the critical transition.

In contrast, global characteristics of CP-based TEFNs are modified differently during the critical transition. Lower values of $L$ and higher values of $C$ indicate the formation of more clustered structures within the TEFNs. Furthermore, and unlike SF-based TEFNs, the stability of the globally synchronized state decreases during the critical transition.

It is important to note that, for SW-based TEFNs, the average shortest path length ($L$) and global clustering coefficient ($C$) during critical transitions are comparable to those observed during normal dynamics for a smaller subset of SW-based TEFNs (see Fig. 6, second-order peak of $L$ and $C$ during normal dynamics, shown in gray). For this subset, the networks appear to reflect a densely connected large core during periods of normal dynamics, in contrast to more weakly connected smaller clusters seen in CP-based TEFNs. A similar observation is made for the shortest path length ($L$) in SF-based TEFNs.

This overall highlights specific structural properties of SW- and SF-based TEFNs, which often exhibit characteristics of densely connected networks, potentially facilitating the occurrence of critical transitions.

*Interpretation.* The schematics shown in Fig. 7 summarizes our findings based on the occurrence of tipping constituents and differences observed in local and global network characteristics. During periods of normal dynamics, the tipping subnetwork already tends to be overall more integrated in the time-evolving functional network than the nontipping subnetwork. We observe this difference of integration in TEFNs irrespective of the coupling topologies of the excitable complex networks.

For CP-based TEFNs in the critical transition, the tipping subnetwork is gradually (with the tipping subnetwork viewed as the core of the TEFN) and globally weaker integrated, while yet being locally, and with respect to certain path structures, more strongly integrated. This modification is clearly more pronounced for the tipping subnetwork than for the nontipping one and resembles the formation of a more structured topology within the

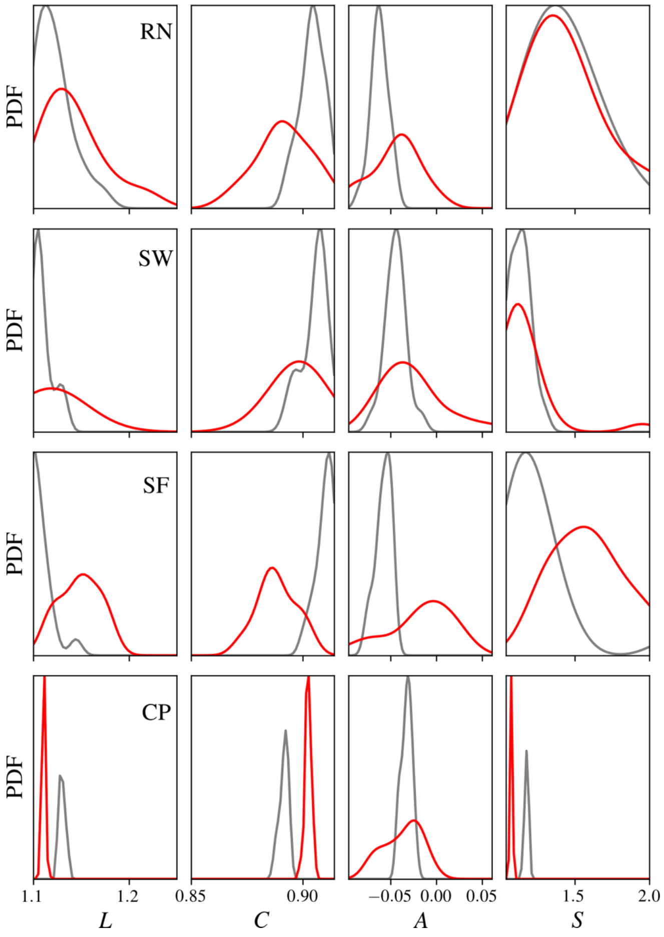

FIG. 6. Probability density functions (PDFs) of median (over time) global characteristics of time-evolving functional networks (TEFNs) during periods of normal dynamics (gray) and during critical transitions (red). TEFNs were derived from excitable complex networks with a random (RN), small-world (SW), scale-free (SF), or all-to-all (CP) coupling topology. Average shortest path length $L$, global clustering coefficient $C$, assortativity $A$, and synchronizability $S$.

TEFNs, exhibiting features of scale-free and small-world networks.

For SW-/SF-, and RN-based TEFNs in the critical transition, we observe opposing modifications. The variability of how tipping elements are structurally integrated is reduced, and the amount of weakly and strongly integrated elements becomes more comparable. Both these modifications indicate a homogenization of the structural integration of constituents of the tipping subnetwork within the TEFN. Further, and in comparison to the nontipping subnetwork, the tipping one is locally less integrated with an apparent lack of certain path structures, while being globally more integrated within the TEFNs in the critical transition. Contrasting the observations made for CP-based TEFNs, this points towards a counterbalancing of the topological properties of the TEFNs, bringing them closer to a rigid network (cf. Refs. [71–74]).

Summarizing this section, we identified subnetworks within time-evolving complex networks of coupled excitable FitzHugh-Nagumo oscillators. These subnetworks are characterized by their distinct structural integration into the larger networks. During a critical transition to an extreme event, the subnetworks are modified in their relevant global and local topological properties, such that they oppose those of the excitable complex networks' coupling topology. These modifications of a subnetwork to a tipping one are essential for the generation of patterns of local temporal precursors (protoevents) and for a buildup of a critical mass of such patterns of precursors that eventually culminates into an extreme event.

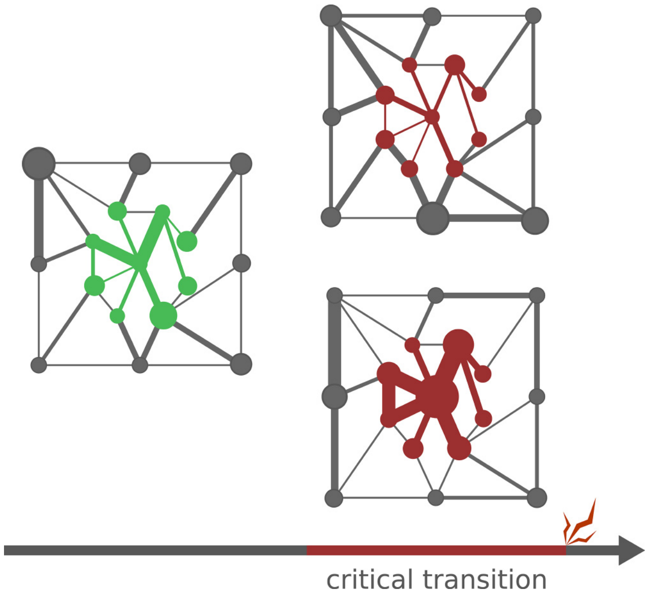

FIG. 7. Schematic of average structural integration of the tipping and the nontipping subnetwork (constituents in gray) within a time-evolving functional network (TEFN) transiting from normal dynamics (constituents of tipping network in green) via a critical transition (constituents of tipping network in red) to an extreme event. The structural integration for CP-based TEFNs (right top) differs from the ones for SW-/SF- or RN-based TEFNs (right bottom). Size/thickness of constituents encodes their structural integration, with larger constituents being overall more strongly integrated.

### B. Tipping subnetwork in the human epileptic brain

There is strong evidence for the extreme event epileptic seizure [75] to be preceded by a long-lasting critical transition [67], although the exact mechanisms underlying seizure generation are not yet fully understood. A critical transition can often be detected as gradual but enduring changes in interaction patterns between different regions of the brain [68], which suggests the brain's large-scale organization to play a crucial role in seizure generation. Indeed, temporal changes in the structural integration of a TEFN's constituents into the larger network point to widespread network reconfigurations associated with a critical transition into an epileptic seizure [76]. Since these changes also identify individual vertices as local tipping elements [77], and given the commonalities of these observations with the ones made for excitable complex networks we propose that these tipping vertices are part of a tipping subnetwork, that may drive network reconfiguration during the critical transition into a seizure.

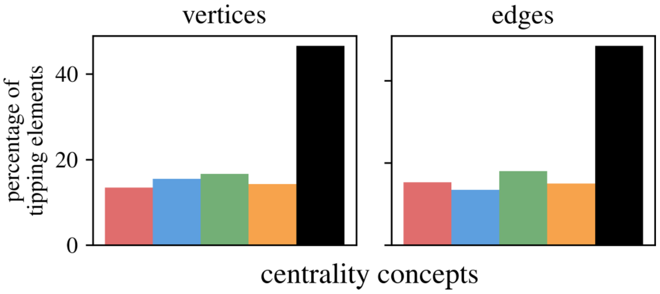

FIG. 8. Relative amount of tipping elements in time-evolving functional networks for which any vertices or any edges were identified as tipping elements, with the structural integration of tipping elements (vertices or edges) quantified with different centrality concepts (color coded). Centrality concepts (Appendix B): $\mathcal{C}^{\mathrm{B}}$ (red); $\mathcal{C}^{\mathrm{C}}$ (blue); $\mathcal{C}^{\mathrm{E}}$ (green); $\mathcal{C}_{\mathrm{v}}^{\mathrm{S}}/\mathcal{C}_{\mathrm{e}}^{\mathrm{N}}$ (orange); with any of the concepts (black), including any constituent that has been deemed a tipping element based on either one or possibly multiple centrality measures.

*Occurrence of tipping constituents.* Proceeding with the methodological steps from Sec. III, we identify tipping vertices in the TEFNs (average network size $V = 50$) from all but one subject and tipping edges in all subjects during the critical transition to an epileptic seizure (Fig. 8).

On average, about half of the TEFNs' constituents (47% of vertices and 49% of edges) are tipping elements, and we note that the majority of them do not coincide with constituents identified clinically as the so-called seizure onset zone [78]. For either of the subjects, connected to all of the identified tipping vertices is at least one tipping edge. In contrast, only about half of the tipping edges connect two tipping vertices and about one-quarter connect to only one tipping vertex, on average. Figure 9 provides a comprehensive overview of median changes. Overall, we identify a tipping subnetwork in all but one subject. It consists of about half of the TEFNs' tipping constituents, on average, and spans different brain lobes and both brain hemispheres. The remaining tipping constituents do not form any other structure of somewhat comparable size and are liberally connected to the nontipping subnetwork.

*Structural integration assessed with strength-based centrality concepts.* During normal dynamics, median vertex strength centrality ($\mathcal{C}_{\mathrm{v}}^{\mathrm{S}}$) is higher in the tipping subnetwork than in the nontipping subnetwork. However, during critical transitions, this relationship reverses. Specifically, the tipping subnetwork has higher median $\mathcal{C}_{\mathrm{v}}^{\mathrm{S}}$ value during normal dynamics than during the critical transition, whereas the nontipping subnetwork shows the opposite pattern.

For nearest-neighbor edge centrality ($\mathcal{C}_{\mathrm{e}}^{\mathrm{N}}$), the trend is reversed. During normal dynamics, the median $\mathcal{C}_{\mathrm{e}}^{\mathrm{N}}$ in the tipping subnetwork is smaller than in the nontipping subnetwork. In contrast, during the critical transition, median $\mathcal{C}_{\mathrm{e}}^{\mathrm{N}}$ is larger in the tipping subnetwork and smaller in the nontipping subnetwork. Overall, during the critical transition, median $\mathcal{C}_{\mathrm{e}}^{\mathrm{N}}$ is higher in the tipping subnetwork than in the nontipping subnetwork.

For vertex eigenvector centrality ($\mathcal{C}_{\mathrm{v}}^{\mathrm{E}}$), the median is consistently larger in the tipping subnetwork than in the nontipping subnetwork, both during normal dynamics and the critical transition. However, median $\mathcal{C}_{\mathrm{v}}^{\mathrm{E}}$ in the tipping subnetwork is lower during the critical transition compared to normal dynamics, while the opposite is true for the nontipping subnetwork.

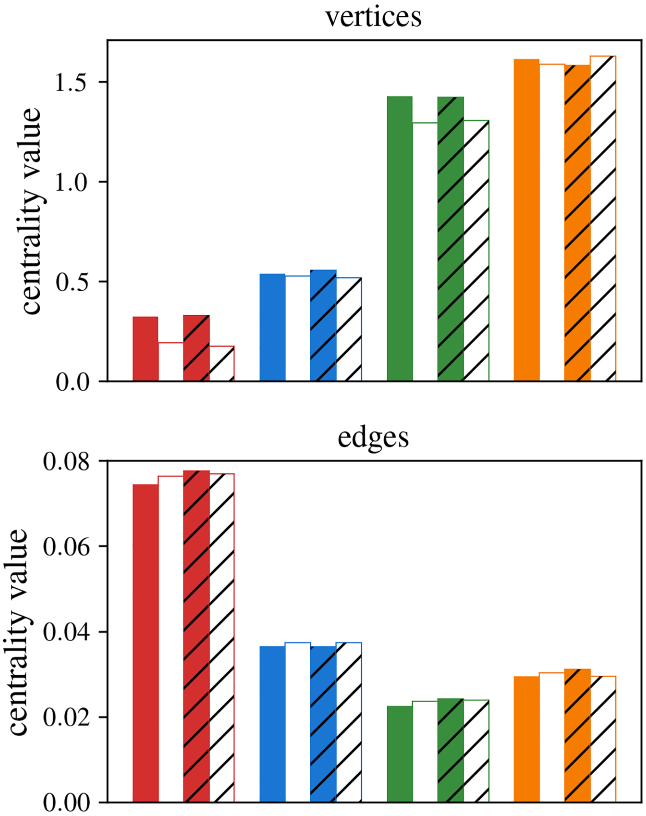

FIG. 9. Same as Fig. 5 but results for time-evolving functional brain networks. Centrality concepts (Appendix B) are color coded: betweenness $\mathcal{C}^{\mathrm{B}}$ (red); closeness $\mathcal{C}^{\mathrm{C}}$ (blue); eigenvector $\mathcal{C}^{\mathrm{E}}$ (green); strength/nearest neighbor $\mathcal{C}_{\mathrm{v}}^{\mathrm{S}}/\mathcal{C}_{\mathrm{e}}^{\mathrm{N}}$ (orange). We rescaled median centrality values for easier legibility of the figure [scaling factors for vertex centralities: $(\mathcal{C}^{\mathrm{B}}, \mathcal{C}^{\mathrm{C}}, \mathcal{C}^{\mathrm{E}}, \mathcal{C}_{\mathrm{v}}^{\mathrm{S}}) = (100, 100, 10, 0.01)$; scaling factors for edge centralities: $(\mathcal{C}^{\mathrm{B}}, \mathcal{C}^{\mathrm{C}}, \mathcal{C}^{\mathrm{E}}, \mathcal{C}_{\mathrm{e}}^{\mathrm{N}}) = (100, 0.01, 1, 1)$].

In contrast to the previous centralities, the changes of the median edge eigenvector centrality ($\mathcal{C}_{\mathrm{e}}^{\mathrm{E}}$) differ. During normal dynamics, median $\mathcal{C}_{\mathrm{e}}^{\mathrm{E}}$ is slightly higher in the nontipping subnetwork than in the tipping subnetwork. However, during the critical transition, median $\mathcal{C}_{\mathrm{e}}^{\mathrm{E}}$ in the tipping subnetwork exceed the one in the nontipping subnetwork, with the nontipping subnetwork being more similar to the one during normal dynamics.

Overall, these observations suggest that the tipping subnetwork becomes more strongly connected within itself during the critical transition compared to normal dynamics. This indicates that during the critical transition, the tipping subnetwork is less interconnected with the nontipping subnetwork.

*Structural integration assessed with path-based centrality concepts.* During normal dynamics, the median vertex closeness centrality ($\mathcal{C}_{\mathrm{v}}^{\mathrm{C}}$) in the tipping and nontipping subnetworks is similar. However, during the critical transition, the tipping subnetwork exhibits slightly higher median $\mathcal{C}_{\mathrm{v}}^{\mathrm{C}}$, while the nontipping subnetwork shows a slightly smaller median $\mathcal{C}_{\mathrm{v}}^{\mathrm{C}}$. Median edge closeness centrality ($\mathcal{C}_{\mathrm{e}}^{\mathrm{C}}$) is comparable in both subnetworks during normal dynamics and the critical

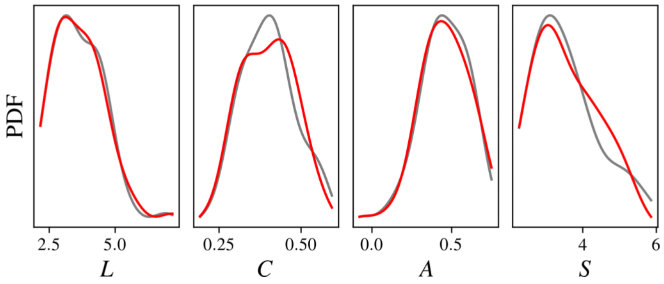

FIG. 10. Same as Fig. 6 but results from time-evolving functional brain networks.

transition, with only minuscule differences observed between the two periods.

For the vertex betweenness centrality ($\mathcal{C}_\text{v}^\text{B}$), the median is higher in the tipping subnetwork compared to the nontipping subnetwork during normal dynamics. This difference becomes more pronounced during the critical transition, where the median $\mathcal{C}_\text{v}^\text{B}$ in the tipping subnetwork increases further, while the median $\mathcal{C}_\text{v}^\text{B}$ in the nontipping subnetwork slightly decreases. A similar difference is observed for edge betweenness centrality ($\mathcal{C}_\text{e}^\text{B}$) in the tipping subnetwork, where the median $\mathcal{C}_\text{e}^\text{B}$ is higher during the critical transition than during normal dynamics. In contrast, the median $\mathcal{C}_\text{e}^\text{B}$ in the nontipping subnetwork is slightly higher during the critical transition compared to normal dynamics.

These findings align with the changes observed in strength-based vertex and edge centralities. However, during the critical transition, the differences between the tipping and nontipping subnetwork further emphasize the presence of distinct path structures in these subnetworks, highlighting their unique characteristics.

Overall, the observed changes in structural integration, as assessed with strength- and path-based vertex and edge centralities, point to a stark contrast between the subnetworks, suggesting a potential sheltering effect in which the tipping subnetwork becomes more isolated from the nontipping one and vice versa.

*Topological and spectral characteristics.* We observe only minuscule differences in the global characteristics of TEFNs from epileptic brain networks when comparing normal dynamics and critical transitions [79]. These differences do not contrast with, nor do they emphasize the trends observed in the changes in centralities (Fig. 10; [80]).

*Interpretation.* During periods of normal dynamics, especially the tipping vertices are already more structurally integrated into the TEFN than other vertices, but the contrary is true for tipping edges (cf. Fig. 11). Although the latter points to a weak intrinsic connectedness of the tipping subnetwork's constituents, despite being generally integrated into the TEFN, it nevertheless emphasizes the possibility of distinguishing between the tipping and the nontipping subnetwork already during periods of normal dynamics.

The distinction becomes more apparent during the critical transition (Fig. 11), as the intrinsic connectedness within the tipping subnetwork is increased while its general structural integration into the TEFN and compared to the nontipping subnetwork is decreased. The formation of path structures within the latter further contrasts the tipping subnetwork. These alterations of the TEFN can overall be abstracted as a sheltering of the tipping subnetwork from the remaining network, making the tipping subnetwork more rigid during the critical transition. We note that these alterations of the TEFN during the critical transition do not entail, on average, any alterations of its global properties. This underlines the crucial importance of substructures involved in the critical transition, but whose alterations can be compensated for at the global level.

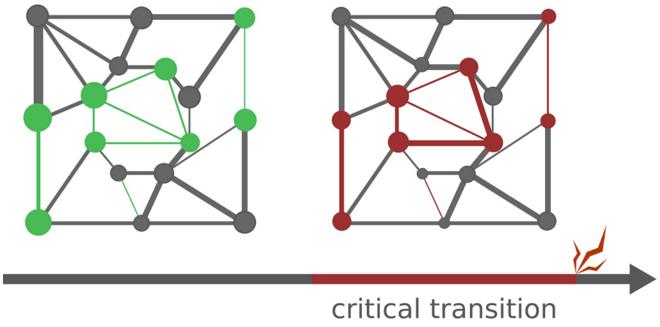

FIG. 11. Schematic of average structural integration of the tipping and the nontipping subnetwork (constituents in green and gray, respectively) within a time-evolving functional brain network transiting from normal dynamics (left) via a critical transition (right; constituents of tipping network in red) to the extreme event epileptic seizure. Size/thickness of constituents encodes their structural integration, with larger/thicker constituents being overall more strongly integrated.

Summarizing this section, we conclude that a tipping subnetwork is also detectable in a natural networked dynamical system undergoing a critical transitions to an extreme event. We observe commonalities between a tipping subnetwork in the human epileptic brain and the tipping subnetworks identified in complex networks composed of FitzHugh-Nagumo oscillators (Sec. IV A), and differences may be attributable to the specifics of the investigated systems.

## V. DISCUSSION

We report on tipping subnetworks associated with critical transitions preceding extreme events in complex networked systems. The tipping subnetwork consists of specific constituents of the corresponding functional network, tipping vertices, and tipping edges, whose time-dependent properties carry information about an impending extreme event. As parts of the larger complex networked system, the tipping subnetwork contrasts the nontipping one in its significantly different temporal alterations of its structural integration. Although these alterations vary for the investigated systems, they exhibit general similarities. Overall, tipping subnetworks tend to be more rigid during critical transitions and hence less susceptible to (possibly unobserved) dynamics unrelated to potential generating mechanisms of an extreme event.

Critical transitions are omnipresent and can be observed in the dynamics of a wide range of natural and man-made complex systems. Understanding, predicting, and potentially altering these transitions is crucial, as their often disastrous impact on both the system and its environment can have far-reaching consequences. The success in predicting extreme events is still limited and highly depends on the investigated system [3,7,15,81–90].

Shifting the focus from a global or unit-centric view to one that emphasizes the role and relevance of complex interaction structures, our study provides additional information about potential mechanisms involved in the generation of extreme events, in both, the investigated toy models and the human epileptic brain.

It is evident that the tipping subnetwork plays a crucial role in the mechanisms underlying critical transitions. The properties of the tipping subnetwork appear to exhibit, and possibly need to fulfill, distinct characteristics that enable mechanisms such as amplification and excitation to occur. These characteristics are generally associated with a reinforced interconnectedness within the tipping subnetwork, which, in turn, contributes to the preservation of these properties, possibly via positive feedback [91,92]. This interconnectedness ultimately renders the tipping subnetwork more rigid, a feature that may be essential for the system to tip into a critical state.

Our findings imply that mechanisms associated with critical transitions can be studied in greater detail within the tipping subnetwork due to it being less influenced by other dynamics, which results from its seclusion from the larger network. This can aid in the development of more refined mathematical models of critical transitions in complex networked systems and in advancing existing or developing novel time-series-analysis techniques for their detection, characterization, and possibly prediction. Indeed, our study further indicates that the relative sizes of the tipping and nontipping subnetwork differ for the investigated systems. This may be due to the different systems' dynamics, as, apart from toy models, access to their full spatial and temporal extend might be limited, especially in natural systems. Yet, in the context of emergent phenomena, such as critical transitions, sufficient knowledge about subsystems and their dynamics is mandatory. Incomplete or insufficient spatial and temporal sampling can lead to severe misinterpretations of network properties [93–101] and their time-dependent changes, possibly restricting the assessment of tipping elements to only a fraction. Further research is necessary to find appropriate solutions to these as of yet unsolved issues, but we are confident that future online detection and characterization of tipping subnetworks can greatly aid in tackling challenges associated with predicting, mitigating and even preventing critical transitions and extreme events.

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## DATA AVAILABILITY

The data of research participants that support the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available as they contain information that could compromise the privacy of research participants.

## APPENDIX A: EEG DATA

Electroencephalographic signals (EEG) were recorded continuously over prolonged periods, typically covering several days, from 48 adult subjects as part of the presurgical evaluation of intractable epilepsies. Recordings captured, on average, 2.3 clinical seizures per subject (range: 1–7; total: 123; we neglected subclinical seizures in our analyses).

The study was approved by the ethics committee of the University of Bonn and each subject had signed informed consent that their data could be used and published for research purposes. All experiments were performed in accordance with relevant guidelines and regulations.

EEG were recorded from electrodes implanted bilaterally under the skull and into deeper structures of the brain, hence with a high signal-to-noise ratio. Subdural strip electrodes consisted of four or eight contacts with an intercontact distance of 10 mm, and subdural grid electrodes had $8 \times 4$ or $8 \times 8$ contacts with an intercontact distance of 10 mm. Pairs of needle-shaped depth electrodes were each equipped with ten or eight cylindrical contacts of length 2.5 mm and an intercontact distance of 4 mm. Number and anatomical locations of electrodes were adapted to the subjects' needs and were thus highly nonuniform (average number of contacts: $V = 50$, range: 14–120).

EEG data were digitally filtered in the frequency band 1 Hz–45 Hz, sampled at 200 Hz (sampling interval 5 ms) using a 16-bit analog-to-digital converter and referenced against the average of two electrode contacts outside of the presumed focal region. These reference contacts were hence chosen individually for each subject, and their data was disregarded in this study.

## APPENDIX B: QUANTIFYING THE STRUCTURAL INTEGRATION OF NETWORK CONSTITUENTS

The structural integration of a single constituent (vertex, edge) within a network can be quantified using centrality concepts, where the quantification can be based on several different network aspects [102–104]. We here employ four different centrality concepts, jointly defined for vertices and edges [105,106], differentiating between strength-based concepts (strength/nearest-neighbor centrality and eigenvector centrality) and path-based concepts (closeness centrality and betweenness centrality). Within each group, the former concepts are more sensitive to local aspects of the network, while the latter concepts are more sensitive to global aspects.

### 1. Strength-based centrality concepts

Strength centrality (or just strength $s$) of vertex $z$ in a weighted network is the sum of weights of all edges connected to this vertex (its analog in a binary network is the degree):

$$\mathcal{C}_{\mathrm{v}}^{\mathrm{S}}(z) = s(z) = \sum_{l=0}^{V} \mathcal{W}_{zl}. \tag{B1}$$

Strength and degree have been generalized to derive a strength-based centrality concept for an edge, called nearest-neighbor edge centrality [106]. With this concept, an edge is considered to be more central the larger its weight and the more similar and the higher the strengths of the vertices which are connected by that edge. Nearest-neighbor edge centrality of edge $z$ between vertices $m$ and $n$ is defined as:

$$\mathcal{C}_{\mathrm{e}}^{\mathrm{N}}(z) = \frac{\mathcal{C}_{\mathrm{v}}^{\mathrm{S}}(m) + \mathcal{C}_{\mathrm{v}}^{\mathrm{S}}(n) - 2w(z)}{\left|\mathcal{C}_{\mathrm{v}}^{\mathrm{S}}(m) - \mathcal{C}_{\mathrm{v}}^{\mathrm{S}}(n)\right| + 1}\, w(z), \tag{B2}$$

where $w(z) = \mathcal{W}_{mn}$ denotes the edge weight and $z \in \{1, \ldots, E\}$ and $(m, n) \in \{1, \ldots, V\}$. Much like strength centrality of a vertex, nearest-neighbor centrality of an edge is only influenced by its adjacent network constituents.

With the concept of eigenvector centrality, a network constituent is central if its adjacent constituents of the same type are also central. This concept thus considers the influence of a vertex/edge (v/e) on the network as a whole. Eigenvector centrality of vertex [107] or edge [105] $z$ is defined as the $z$th entry of the eigenvector $\mathbf{v}$ corresponding to the dominant eigenvalue $\lambda_{\max}$ of matrix $\mathbf{M}$, which can be derived from the eigenvector equation $\mathbf{Mv} = \lambda\mathbf{v}$ using the power iteration method:

$$\mathcal{C}_{\mathrm{v,e}}^{\mathrm{E}}(z) = \frac{1}{\lambda_{\max}} \sum_{l} M_{zl}\, \mathcal{C}_{\mathrm{v,e}}^{\mathrm{E}}(l). \tag{B3}$$

In case of vertices, $\{z, l\} \in \mathcal{V}$ and $\mathbf{M}$ denotes the weight matrix $\mathcal{W}^{(\mathrm{v})} \in [0, 1]^{V\times V}$, with $\mathcal{W}_{zl}^{(\mathrm{v})}$ denoting the weight of an edge between vertices $z$ and $l$. We define $\mathcal{W}_{zz}^{(\mathrm{v})} := 0\,\forall\, z$ with $z \in \{1, \ldots, V\}$. In case of edges, $\{z, l\} \in \mathcal{E}$ and $\mathbf{M}$ denotes the weight matrix $\mathcal{W}^{(\mathrm{e})} \in [0, 1]^{E\times E}$ whose entries $\mathcal{W}_{zl}^{(\mathrm{e})}$ are assigned the average weight of edges $z$ and $l$ if these edges are connected to a same vertex, and 0 otherwise. As above, we define $\mathcal{W}_{zz}^{(\mathrm{e})} := 0\,\forall\, z$ with $z \in \{1, \ldots, E\}$.

### 2. Path-based centrality concepts

A path between two network constituents $m$ and $n$ is defined as the set of edges that have to be traversed in order to get from $m$ to $n$ or vice versa. The length of a path can be defined as the sum of the inverse weights of edges along this path. A path is considered short (or strong) if this sum is small; it is considered long (or weak) if this sum is large. In this context, a path structure refers to the arrangement or configuration of paths within the network, which can be used to assess aspects such as the number of shortest paths, information flow, or the overall connectedness of the network.

The concept of closeness centrality considers the distances (length of the respective shortest paths) between a constituent and all other constituents in a network. A constituent with a high closeness centrality is central as information from this constituent can reach all other constituents in the network via short paths, and so the constituent can exert a more direct influence over the network. Closeness centrality of vertex $z$ is defined as [108]:

$$\mathcal{C}_{\mathrm{v}}^{\mathrm{C}}(z) = \frac{V - 1}{\sum_{l} d_{zl}}, \tag{B4}$$

with $(z, l) \in \{1, \ldots, V\}$ and where $d_{zl}$ is the length of the shortest path between vertices $z$ and $l$.

Closeness centrality of edge $z$ between vertices $m$ and $n$ can be defined as [105]:

$$\begin{aligned}\mathcal{C}_{\mathrm{e}}^{\mathrm{C}}(z) &= \frac{E - 1}{\sum_{l} (d_{lm} + d_{ln})} = \frac{E - 1}{\frac{1}{\mathcal{C}_{\mathrm{v}}^{\mathrm{C}}(m)} + \frac{1}{\mathcal{C}_{\mathrm{v}}^{\mathrm{C}}(n)}}\\ &= (E - 1)\frac{\mathcal{C}_{\mathrm{v}}^{\mathrm{C}}(m)\,\mathcal{C}_{\mathrm{v}}^{\mathrm{C}}(n)}{\mathcal{C}_{\mathrm{v}}^{\mathrm{C}}(m) + \mathcal{C}_{\mathrm{v}}^{\mathrm{C}}(n)},\end{aligned} \tag{B5}$$

with $z \in \{1, \ldots, E\}$ and $(m, n, l) \in \{1, \ldots, V\}$.

The concept of betweenness centrality considers the frequency of shortest paths traversing a given constituent. A constituent with a high frequency of traversings (high betweenness centrality value) acts as a bridge between other parts of the network and can thus be considered a central constituent. Vertex/edge betweenness centrality (of vertex/edge $z$) can be defined as [105,109–111]

$$\mathcal{C}_{\mathrm{v,e}}^{\mathrm{B}}(z) = \frac{2}{F} \sum_{l \neq m} \frac{q_{lm}(z)}{G_{lm}}, \tag{B6}$$

where $z \in \{1, \ldots, V\}$ (for vertices) $[z \in \{1, \ldots, E\}$ (for edges)], $\{l, m\} \in \{1, \ldots, V\}$, $q_{lm}(z)$ is the number of shortest paths between vertices $l$ and $m$ running through vertex/edge $z$, and $G_{lm}$ is the total number of shortest paths between vertices $l$ and $m$. As above, we define the length of a path as the sum of the inverse of all edge weights on that path. The normalization factor is $F = (V - 1)(V - 2)$ in case of vertices and $F = V(V - 1)$ in case of edges.

In general, a high (low) centrality value indicates a strong (weak) structural integration of a constituent within a network. Calculating the aforementioned centralities of each network constituent in the time-dependent sequence of functional snapshot networks (Sec. III A), we derive time-dependent sequences of centrality values that allow tracking temporal alteration of a constituent's structural integration far off and during critical transition.

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# The time-evolving epileptic brain network: concepts, definitions, accomplishments, perspectives

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Epilepsy is now considered a network disease that affects the brain across multiple levels of spatial and temporal scales. The paradigm shift from an epileptic focus—a discrete cortical area from which seizures originate—to a widespread epileptic network—spanning lobes and hemispheres—considerably advanced our understanding of epilepsy and continues to influence both research and clinical treatment of this multi-faceted high-impact neurological disorder. The epileptic network, however, is not static but evolves in time which requires novel approaches for an in-depth characterization. In this review, we discuss conceptual basics of network theory and critically examine state-of-the-art recording techniques and analysis tools used to assess and characterize a time-evolving human epileptic brain network. We give an account on current shortcomings and highlight potential developments towards an improved clinical management of epilepsy.

KEYWORDS

**epilepsy, epileptic network, epileptic focus, seizure, seizure-prediction, seizure-control, electroencephalography, brain dynamics**

## 1 Introduction

Epilepsy is the third most common neurological disorder with a worldwide prevalence of about 1% (Beghi et al., 2019; World Health Organization [WHO], 2019). Epilepsy is clinically diagnosed by multiple epileptic seizures or by an epilepsy syndrome or by a single seizure and a probability of at least 60% for further seizures to occur over the next 10 years (Fisher et al., 2005). An epileptic seizure is defined as a transient occurrence of symptoms due to abnormal excessive or synchronous neuronal activity in the brain (Fisher et al., 2005). It can appear due to an acute disease of the brain (e.g., acute symptomatic seizures due to brain abscess), due to systemic disorders (i.e., metabolic disturbances), or as a symptom of a chronic disease, i.e., epilepsy. The disease can be treated sufficiently well in about two-thirds of people with epilepsy (Kwan and Brodie, 2000; Chen et al., 2018), while the other third needs intensive diagnostics and extensive therapy attempts such as non-pharmaceutical interventions (e.g., resective epilepsy surgery, neurostimulation) which in some cases are associated with significant risks or side effects. The people's willingness to undergo more difficult or risky therapies depends on the burden of the disease being treated. The burden of epilepsy is composed of several factors: comorbidities (Mesraoua et al., 2020), psychosocial impairment, social stigma (Kwon et al., 2022), medico-legal restriction, direct and indirect costs (Strzelczyk et al., 2008; Allers et al., 2015) and—as to be expected—seizures, their treatment and potential complications (Noe, 2019; Mesraoua et al., 2020). The apparent unpredictability of most seizures not only increases the risk of injuries and discomfort, but also imposes loss of autonomy, fear of seizures as well as psychosocial stress (Lang et al., 2022), thereby impacting massively on the quality of life of those affected and their caregivers (Baker et al., 1997; Chiang et al., 2020; Strzelczyk et al., 2023). Thus understanding emergence, propagation, and cessation of epileptic seizures is generally assumed to be crucial to understand the nature of epilepsy, and to understand and establish diagnostic approaches as well as treatment options.

Classification of seizures, epilepsies, and epilepsy syndromes changed over time (Merlis, 1970; Dreifuss et al., 1985; Commission on Classification and Terminology of the International League Against Epilepsy, 1989; Berg and Scheffer, 2011), and an increasingly sophisticated work-up was demanded in clinical daily practice to better understand, characterize, and treat the disease. Moreover, the dichotomy of focal and generalized epilepsy was questioned (Lüders et al., 2009). In the clinical context, the origin of epileptic seizures has been inferred firstly from structural changes and secondly from semiology, i.e., behavioral changes during a seizure. Electrophysiological changes associated with behavioral changes were used as a bridge for diagnosis and referred to as “ictal patterns”. This led to the model of a focal seizure origin and, for a long time, to assignments of involved brain regions to the different zones in presurgical epilepsy diagnosis (symptomatogenic zone, irritative zone, seizure onset zone, epileptogenic lesion, epileptogenic zone, eloquent cortex) (Rosenow and Lüders, 2001). Follow-up data, however, demonstrated that only a portion of subjects treated with focal therapies such as epilepsy surgery (Téllez-Zenteno et al., 2005) or focal brain stimulation achieves long-term seizure freedom (Simpson et al., 2022), which raises doubts about the usefulness of the concept of a focal seizure origin. Furthermore, a similar cerebral lesion does not cause seizures in every subject, so a “proconvulsive” disposition must be suspected.

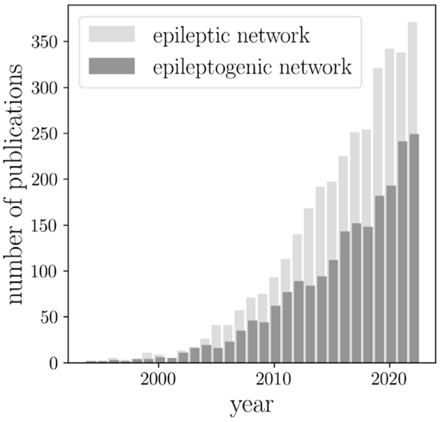
The epileptic brain should not be viewed as a temporarily disturbed normal brain since it differs from a normal brain in many structural and functional aspects, and seizures take up only a small fraction of a subject’s lifetime. Function and dysfunction of the adaptive dynamical system epileptic brain are interacting processes that cover various time scales and are influenced by various endogenous and exogenous factors. These range from seizures and biological rhythms to treatments with antiseizure medication, neurostimulation, or epilepsy surgery. Moreover, the brain’s dynamics are influenced by its intricate structural complexity; due to its intrinsic plasticity and adaptiveness, dynamics can modify structure (Sporns, 2022). Together, this calls for sophisticated approaches to improve our understanding of the epileptic brain’s complex structure-(dys)functions relationship.

Research over the last decades has demonstrated the excellent suitability of the network approach to the complex system brain in health and disease (Bullmore and Sporns, 2009; 2012; Avena-Koenigsberger et al., 2018). The explicit time-dependence of the epileptic brain, however, required an additional change in perspective from a static to a time-evolving network. We here review this novel perspective, its concepts, definitions, and accomplishments, and discuss possible translations into clinical practice.

## 2 Conceptual considerations

In her seminal work, Susan Spencer considered *a network to be a functionally and anatomically connected, bilaterally represented, set of cortical and subcortical brain structures and regions in which activity in any one part affects activity in all the others. The essential operational component of this definition is the observation that vulnerability to seizure activity in any one part of the network is influenced by activity everywhere else in the network, and that the network as a whole is responsible for the clinical and electrographic phenomena that we associate with human seizures. Implicit in this idea is that the seizures may entrain this large neural network from any given part, such that it becomes irrelevant to discuss the “onset” of seizures in any specific part of the network. In other words, the electrical hyperexcitability associated with seizure activity reverberates within the neural structures of the network, which operate together and inextricably to culminate in the eventual expression of seizures* (Spencer, 2002).

BOX 1 The number of papers on epileptic brain network published during the past three decades (sourced via Google Scholar using the keywords “epileptic network” and “epileptogenic network”).



Since then, epileptic brain network studies (sometimes also referred to as an epileptogenic network) increased by almost a factor of 30 (Box 1). In 2010, the term *network* was included in the revised terminology and concepts for organization of seizures and epilepsies of the International League against Epilepsy (Berg et al., 2010). This highlighted the transition from the old concepts of an epileptic focus and various cortical zones involved in epilepsy (Rosenow and Lüders, 2001) to an epileptic network spanning lobes and hemispheres. Today, epilepsy is considered a network disease. The progress made in this highly interdisciplinary research field has been repeatedly summarized in a number of reviews [see, e.g. (Richardson, 2010; Kramer and Cash, 2012; Laufs, 2012; Engel et al., 2013; van Diessen et al., 2013; Chiang and Haneef, 2014; Stam, 2014; van Mierlo et al., 2014; Bernhardt et al., 2015; Bartolomei et al., 2017; Zijlmans et al., 2019; Gil et al., 2020; Royer et al., 2022a)]. A large number of studies provided increasing evidence for an epileptic brain network to differ from healthy ones, both structurally (Whelan et al., 2018; Hatton et al., 2020; Larivière et al., 2020; Sisodiya et al., 2022) and functionally (Chavez et al., 2010; Horstmann et al., 2010; Zhang et al., 2011; Richardson, 2012; Caciagli et al., 2014; Chiang et al., 2015; Foit et al., 2020; Pegg et al., 2020; Slinger et al., 2022). Moreover, studies demonstrated that the network approach allows for an improved understanding of the dynamics of seizures [both generalized and focal (Schindler et al., 2007b; Ponten et al., 2007; Kramer et al., 2008; Schindler et al., 2008; Ponten et al., 2009; Zaveri et al., 2009; Kramer et al., 2010; Kuhnert et al., 2010; Wilke et al., 2011; Bialonski and Lehnertz, 2013; Varotto et al., 2012; Burns et al., 2014; Geier et al., 2015a; Geier et al., 2015b; Zubler et al., 2015; Lopes et al., 2018; Rungratsameetaweemana et al., 2022)] and of the complex interplay between the epileptic process and physiologic activities (Kuhnert et al., 2013; Yaffe et al., 2015; Garcia-Ramos et al., 2016; Vecchio et al., 2016; Steiger et al., 2017; Tailby et al., 2018; Yang et al., 2018; Zaveri et al., 2020; Mutti et al., 2022; Roliz and Kothare, 2022), possibly mediated by the same neural substrate.

Some studies [see, e.g., Zijlmans et al. (2019) for an overview] attempted to integrate the concepts of an epileptic focus and of the aforementioned cortical zones into the concept of an epileptic network by considering the former ones as hubs or hub-like structures, i.e., strongly connected (functionally and/or structurally) network components that significantly impact on the network. The characteristic of being strongly connected, however, is only one of many other properties (cf. Section 3.2) that emphasize a network component as important for both structure and function of an epileptic brain network. Studies going beyond hubs or hub-like structures attribute a rather subordinate role to the epileptic focus and zones for seizure dynamics and for the many (patho-)physiologic phenomena seen in between seizures (Geier et al., 2015a; Geier et al., 2015b; Geier and Lehnertz, 2017b; Geier and Lehnertz, 2017a; Bröhl and Lehnertz, 2019; Rings et al., 2019b; Fruengel et al., 2020; Bröhl and Lehnertz, 2022).

In 2003, John Milton and Peter Jung considered epilepsy as a *dynamic disease* and defined an epileptic system as *a dynamic, ever-changing and evolving, distributed system of neurons that controls the onset, propagation, and arrest of epileptic seizures* and coined the term *evolving epileptic network* (Milton and Jung, 2003). This concept initially received only little attention. It regained interest, however, with the fusion of time-series-analysis techniques and graph-theoretical concepts necessary to investigate evolving (or time-dependent/temporal/multiplex/multilayer) networks (Holme and Saramäki, 2012; Boccaletti et al., 2014; Kivelä et al., 2014; Lehnertz et al., 2014; Muldoon and Bassett, 2016) and with the development of techniques that allow recording and storage of spatially extended brain dynamics assessed over extended periods of time (days to weeks and beyond).

# 3 Techniques to assess and characterize a time-evolving brain network

In a brain network and depending on the chosen spatial scale, a vertex may represent a single cell (e.g., neuron), a group of cells (e.g., cortical columns), or a brain region (e.g., parcellated area) and an edge some connection between vertices. If an edge represents a physical/anatomical connection (single synapses, fiber bundles, or groups of fiber bundles), then the network is referred to as *structural network* (Park and Friston, 2013). If an edge represents some functional interaction between vertices (characterized by the interaction's strength, direction, and functional form), then the network is called a *functional network* (Park and Friston, 2013).

## 3.1 Recording the brain's structure and dynamics

Various imaging and recording techniques can be used to assess structure and dynamics of a time-evolving epileptic brain network on different spatial and temporal scales and with different levels of invasiveness (see Table 1).

Among the structural neuroimaging techniques, x-ray computed tomography (CT) (Ginat and Gupta, 2014; Pelc, 2014) and magnetic resonance imaging (MRI) (Mori et al., 2005; Atlas, 2009) allow the non-invasive study of the whole brain at different levels of spatial resolution, ranging from millimeter-sized voxels to cortical areas and beyond. During the recording, time-dependent structural changes (Fjell and Walhovd, 2010) are assumed to be negligible. Due to a comparatively better differentiability of gray and white matter, particularly MRI and diffusion MRI (Bammer, 2003) are often used to probe the topological organization of the brain (Duncan, 2009; Engel et al., 2013; Duncan et al., 2016; Whelan et al., 2018; Sotiropoulos and Zalesky, 2019; Yeh et al., 2021; Zhang et al., 2022). In a structural network (also referred to as structural connectivity (Horwitz, 2003) or structural connectome), discrete regions of gray matter represent a network's vertices and white matter fibers a network's edges. In order to identify such network constituents, a large number of approaches is employed to parcellate the brain (Eickhoff et al., 2018; Amunts et al., 2020; Bijsterbosch et al., 2020; Royer et al., 2022b) and to identify and characterize white matter fibers (Mori and Van Zijl, 2002; Jeurissen et al., 2019). The variety of techniques requires appropriate approaches to verify and increase the reproducibility of results (Bonilha et al., 2015; Welton et al., 2015; Zalesky et al., 2016; Roine et al., 2019; Lawrence et al., 2021; Alemán-Gómez et al., 2022; Borrelli et al., 2022; Seider et al., 2022; Charvet, 2023; Madole et al., 2023).

Among the functional neuroimaging techniques, positron emission tomography (PET) (Phelps and Mazziotta, 1985; Juhász and Chugani, 2003; Muehllehner and Karp, 2006; Vaquero and Kinahan, 2015; Watabe and Hatazawa, 2019; Seshadri et al., 2021), functional magnetic resonance imaging (fMRI) (Detre, 2004; Buxton, 2013), functional near-infrared spectroscopy (fNIRS) (Jöbsis, 1977; Villringer and Chance, 1997;

**TABLE 1** Structural and (indirect/direct) functional imaging and recording techniques predominantly used to assess structure and dynamics of a time-evolving epileptic brain network (principle: physical mechanisms underlying the measurement; information: information provided by images/time series; n.a. not applicable).

| Structural imaging techniques | | | |
|---|---|---|---|
| | principle | information | resolution |
| Computed tomography (CT) | measure attenuation of X-rays by different tissues; uses ionizing radiation | mean attenuation (relative to water) of tissues in a given pixel/voxel (greyscale-coded) | spatial: ~ $0.5\text{mm}^3$<br>temporal: n.a. |
| Magnetic Resonance Imaging (MRI) | measure magnetization properties of atomic nuclei (mostly hydrogen) employing the techniques of nuclear magnetic resonance; uses strong magnetic field, gradient fields, and radio waves | magnetization properties (e.g., proton density, different relaxation times, diffusion characteristics) of tissues in a given pixel/voxel (greyscale-coded) | spatial: ~ $1\text{mm}^3$<br>temporal: n.a. |
| indirect functional imaging techniques | | | |
| Positron Emission Tomography (PET) | measure changes in metabolic processes and in other physiological activities with radioactive substances (positron emitter) | changes of processes/activities (e.g., cerebral blood flow) per time unit in a given pixel/voxel (color-coded statistical maps) | spatial: 5–10 mm (pixel size)<br>temporal: 5–10 s |
| Functional Magnetic Resonance Imaging (fMRI) | measure brain activity by detecting changes in magnetization properties (T2* relaxation time) of hydrogen associated with blood flow (blood oxygenation-level dependent (BOLD) effect); assumes coupling between cerebral blood flow and neuronal activation | BOLD time series; difference between time series recorded during activation and control condition across the brain or from a specific brain region (color-coded statistical maps) | spatial: 3–4 mm (pixel size)<br>temporal: s |
| Functional Near-Infrared Spectroscopy (fNIRS)/Diffuse Optical Tomography (DOT) | measure brain activity by detecting attenuation (absorption) of near-infrared light associated with blood flow (BOLD effect); assumes coupling between cerebral blood flow and neuronal activation | time series of relative concentration changes in $O_2HB$ and HHb; difference between time series recorded during activation and control condition across the brain or from a specific brain region (color-coded statistical maps) | spatial: 10–20 mm (pixel size)<br>temporal: s |
| direct functional imaging techniques | | | |
| Electroencephalography (EEG) | measure the spontaneous electrical activity (net effect of ionic currents) of the brain as voltage fluctuation at multiple sensors (electrodes) placed on the scalp (non-invasive EEG) or intracranially (invasive EEG) | multiple time series of voltage fluctuations | spatial:<br>sensor space: distance between sensors<br>source space: few mm<br>temporal: ms |
| Magnetoencephalography (MEG) | measure the spontaneous magnetic activity of the brain produced by electrical currents occurring naturally in the brain using very sensitive sensors (e.g., superconducting quantum interferences devices) placed over the head | multiple time series of field fluctuations | spatial:<br>sensor space: distance between sensors<br>source space: few mm<br>temporal: ms |

Ferrari and Quaresima, 2012; Nguyen et al., 2018; Chen et al., 2020), or (high-density) diffuse optical tomography (DOT) (Eggebrecht et al., 2014; Wheelock et al., 2019) can provide non-invasive indirect access to transient neural activity (time scale: some 10 to some 100 milliseconds) by measuring transient changes in cerebral blood flow and/or metabolic processes (time scale: up to some 10 s) assumed to be related to neuronal activation [neurovascular coupling hypothesis; Roy and Sherrington (1890); Huneau et al. (2015); Kaplan et al. (2020); Drew (2022)]. While providing whole-brain coverage, the temporal resolution of these techniques ranges in the order of seconds and is, in general, dictated by the respective imaging device. An exception is MR-encephalography (Hennig et al., 2021), which also allows whole-brain coverage in 100 ms and with a spatial resolution that compares to the other techniques (few millimeters) (Rapisarda et al., 2010; Torricelli et al., 2014; Chaimowet al., 2018). Statistical dependencies (correlation, cross-correlation) between recorded signals from pairs of vertices (from voxels to cortical areas) are often used to define edges of a functional network [also referred to as functional connectivity (Friston, 2011) or functional connectome].

Direct non-invasive access to both transient and ongoing neural activities is achieved with electroencephalography [EEG (Niedermeyer and Lopes da Silva, 2005)] and with magnetoencephalography [MEG (Baillet, 2017)], both of which allow whole-head coverage and have high temporal resolution (few milliseconds). So far, only EEG allows for the continuous recording of brain dynamics over extended periods of time [days to weeks and beyond (Lehnertz et al., 2017; 2021; Milne-Ives et al., 2023)]. This may also be achieved in the future with further improvements of optically-pumped magnetometer

MEG systems (Hill et al., 2019; Boto et al., 2021; Pedersen et al., 2022; Hillebrand et al., 2023). An additional access to the brain's dynamics at the meso- (≈ $10^5$ neurons) and micro-scale (single neurons) can be achieved with invasive (intracranial) EEG (Parvizi and Kastner, 2018; Mercier et al., 2022; Soloukey et al., 2023). Although this approach provides the highest signal-to-noise ratio, it has limited spatial coverage of the brain and is limited to some brain pathologies (such as epilepsy) as it requires electrodes to be implanted (temporarily or chronically) onto the surface (electrocorticography) and/or within the brain (stereo-EEG, local field potentials, single-neuron activity). For EEG recordings, the choice of the reference electrode is a notoriously ill-defined problem (Hagemann et al., 2001; Yao et al., 2005; Zaveri et al., 2006; Rummel et al., 2007; Qin et al., 2010; Geier and Lehnertz, 2017b; Anastasiadou et al., 2019; Yao et al., 2019; Babiloni et al., 2020; Delorme, 2023).

EEG/MEG-based techniques allow to capture a wide spectrum of physiological and pathophysiological activities on various time scales and as such, often require other, more sophisticated time-series-analysis techniques (see Section 3.2) to characterize interactions between the sampled brain regions. Properties of interactions are then used to define edges of a functional network whose vertices are usually associated with sensors (EEG-electrodes, MEG-magnetometers) that capture the dynamics of the sampled neuronal substrate. The number of network vertices may range from

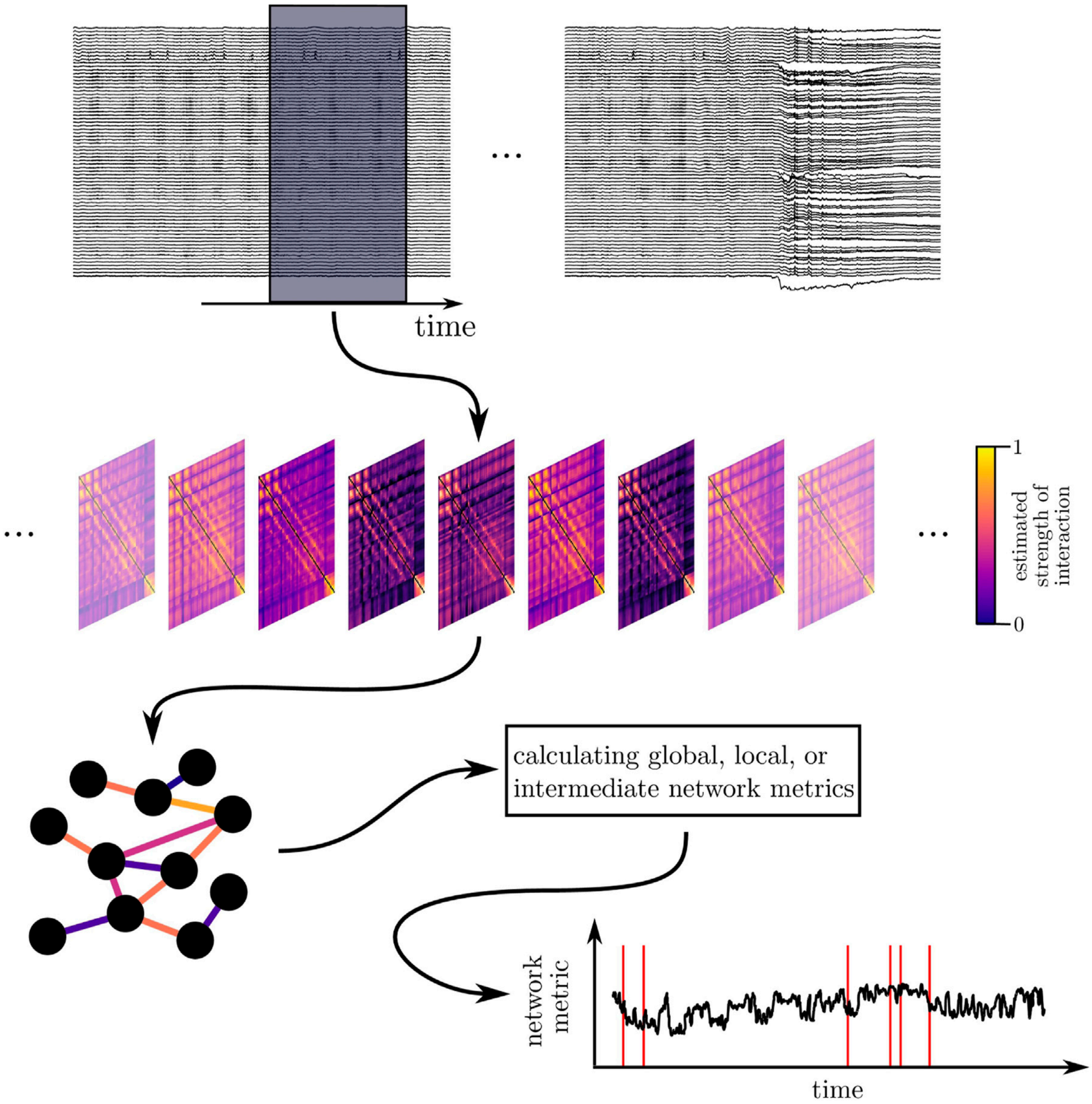


FIGURE 1
Schematic of deriving and characterizing a time-evolving epileptic brain network. Top: sliding-window analysis: long-lasting multichannel EEG recordings are segmented into successive (non-)overlapping windows. Middle: time-dependent sequence of interaction matrices (functional brain networks): each matrix contains estimates of an interaction property (here: strength of interaction) calculated from EEG data within a given window for all pairs of sampled brain regions. Bottom: a network analysis approach renders a time-dependent sequence of a network metric, which is then subject to further analyses. Red lines exemplarily indicate occurrence of epileptic seizures.

a few ten to a few hundred, depending on recording technique and research question. Instead of estimating properties of interactions in *sensor-space*, it has been proposed to do so in *source-space* to overcome the problems of volume conduction (EEG) and field spread (MEG) [see, e.g., van Mierlo et al. (2019); Koutlis et al. (2021); Sadaghiani et al. (2022); Chiarion et al. (2023) and references therein]. Nevertheless, localizing the sources of EEG/MEG activities in the brain constitutes an inverse problem that lacks a unique solution (von Helmholtz, 1853) and source-space-based network approaches continue to be critically discussed (Colclough et al., 2016; Palva et al., 2018; Koutlis et al., 2021; Adamovich et al., 2022; Pourmotabbed et al., 2022; Schaworonkow and Nikulin, 2022; Hatlestad-Hall et al., 2023).

As with the structural neuroimaging techniques, the variety of approaches and methods used in functional network research requires appropriate approaches to verify and increase the reproducibility of results (Niu et al., 2013; Zuo et al., 2014; Zuo and Xing, 2014; Geng et al., 2017; Adamovich et al., 2022; Bottino et al., 2022; Kato et al., 2022; Rolle et al., 2022; Wang et al., 2022; Helwegen et al., 2023). This applies even more to the fusion of structural and functional imaging techniques (Luat and Chugani, 2008; Aiello et al., 2016; Babaeeghazvini et al., 2021; Wu et al., 2021) as well as to the combined use of different functional imaging techniques (e.g., EEG-fNIRS or EEG-fMRI) that is often pursued to balance the disadvantages of one method with the advantages of another method (Machado et al., 2011; Nguyen et al., 2012; Centeno and Carmichael, 2014; Obrig, 2014; Pittau and Vulliemoz, 2015; Tousseyn et al., 2015; Abreu et al., 2018; Sanz-Garcia et al., 2018; Rizkallah et al., 2020; Anderson et al., 2021; Bernabei et al., 2021; Uchitel et al., 2021; Ikemoto et al., 2022; Li et al., 2022; Mulert and Lemieux, 2023).

## 3.2 From observations to a functional brain network

Having recorded the dynamics of various brain regions as multivariate time series, a common way to construct a functional brain network consists of associating network vertices with sampled brain regions and network edges with properties of an interaction (strength, direction, functional form) between pairs of brain regions derived from their dynamics (cf. Figure 1).

The latter ansatz is often pursued in cases where a perturbation-based approach (*actio est reactio*) is either unfeasible or not constructive. Properties of an interaction can then be estimated with diverse linear and nonlinear, bi- and multivariate time-series-analysis techniques grounded in statistics (Rodgers and Nicewander, 1988; Hamilton, 2020), nonlinear dynamics (Kantz and Schreiber, 2003; Datseris and Parlitz, 2022), synchronization theory (Arnhold et al., 1999; Pikovsky et al., 2001; Stankovski et al., 2012; Rosenblum and Pikovsky, 2023), statistical physics (Tabar, 2019), and information theory (Hlaváčková-Schindler et al., 2007), among others.

Given that interactions can manifest themselves in many (also conceptually) different ways (such as the diverse forms of synchronization, flow of information, or similarity) and since there is no *one-fits-all* analysis technique for all types of data or interactions (Pereda et al., 2005; Kreuz et al., 2007; Wendling et al., 2009; Höller et al., 2017), the choice of a time-series-analysis technique is often dictated by the specific research question. Examples of some of the available techniques to estimate properties of interactions are listed in Table 2. Also, depending on the employed recording technique (alongside with the sampling interval; see above), time series can cover various time scales of brain dynamics and include signal properties reflecting different physiological and pathophysiological phenomena. Especially for EEG and MEG recordings, the temporal resolution allows for the separation of the signal into various frequency bands of neural oscillations.

However, spectral limits of brain activity often associated with these frequency bands might vary in time or between brain regions. It also might not be useful to investigate frequency bands without discernible power, while a broader perspective

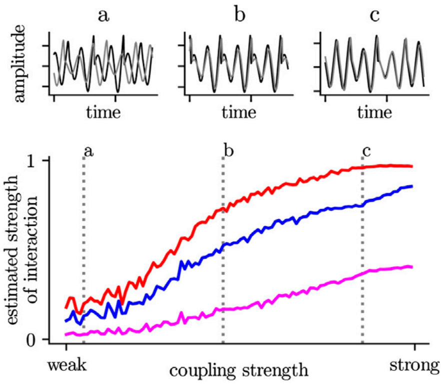
**TABLE 2 Examples of time series analysis techniques used to characterize properties of an interaction based on different signal characteristics. The strength of an interaction quantifies the level of interdependence between two brain regions. Estimators for the strength of an interaction are predominantly based on the idea that more (abstractly) similar dynamics reflect a stronger coupling between regions. The direction of an interaction assesses which of the two interacting brain regions is driving the other. Estimators for the direction of an interaction are usually based on assumptions about cause and effect in the larger system respectively on models for the temporal evolution of the regions' dynamics. The functional form of interaction describes the relationship between two brain regions as a mathematical model. Estimators for the functional form of an interaction have the dual task of setting up an appropriate model for the involved interdependencies and of appraising model parameters, which typically requires strong assumptions and in-depth knowledge of the involved dynamics.**

| Property of interaction | Signal characteristic | Analysis technique |
|---|---|---|
| strength | amplitude | (cross-)correlation |
| | phase | mean phase coherence |
| | information content | mutual information |
| | state space | nonlinear interdependence |
| direction | amplitude | Granger causality |
| | phase | evolution map approach |
| | information content | transfer entropy |
| | state space | nonlinear interdependence |
| functional form | phase | phase dynamics reconstruction |

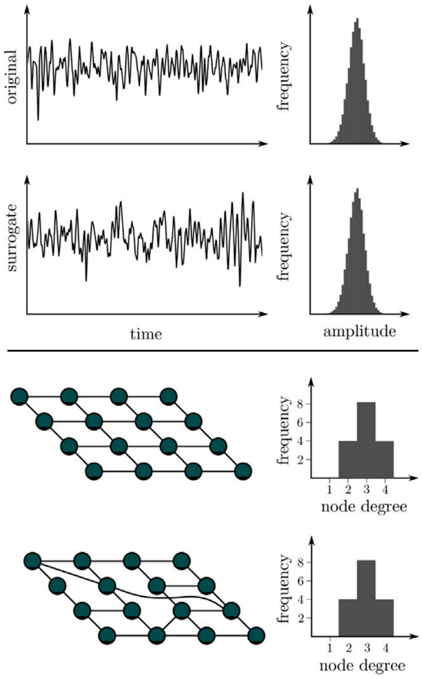
may include otherwise unnoticed phenomena (Osterhage et al., 2007a; Frei et al., 2010; Gerster et al., 2022). In addition, the human brain has to be regarded as an open, dissipative, and adaptive dynamical system and is inherently non-stationary. Most methods to characterize properties of interactions, however, require the system to be (at least approximately) stationary to yield robust and reliable characterizations. Thus, time series of recordings of brain dynamics are typically cut into segments of appropriate duration whose choice is usually a compromise between the required statistical accuracy for the characterization and approximate stationarity within a segment's duration [see Lehnertz et al. (2017) for details]. Together, experimental conditions and handling of the brain's non-stationarity result in the investigation of either carefully-selected segments (possibly influencing findings with selection bias) or of sequences of (non-) overlapping segments or windows (moving-window approach).

Estimates of properties of an interaction can be affected by a number of influencing factors that may arise from specifics of the applied recording techniques, specifics and uncertainties of the various time-series-analysis techniques (cf. Box 2) or due to unavoidable noise contamination. To at least minimize these influences and to improve reliability of estimates, the surrogate approach from statistical hypothesis testing can be employed. This bootstrapping approach begins with formulating an appropriate null hypothesis (Efron, 2004), which specifies properties of influencing factors that might lead to the results of an analysis (cf. Box 3).

BOX 2 The majority of estimators for the strength of an interaction increase non-proportional (i.e., non linear) with an increase of the coupling strength (assuming one knows the true mechanisms for an interaction between two systems (brain regions)). On the one hand, this depends very much on the systems under investigation, but also the choice of the time-series-analysis technique plays an important role. Even in the case of strong coupling, amplitude-based (blue) or information-theory-based estimators (purple) may indicate a low or medium strength of interaction. In contrast, a phase-based estimator (red) already reaches its maximum value. In the first case, the two systems would be interpreted as weakly interacting or even independent, while the second case would indicate a stronger interaction or even a complete alignment (synchronization).



BOX 3 A null model is a statistical model that is built on a null hypothesis. It makes an assumption about a fact, which can be evaluated by way of a statistical test. Using a null model one can test whether analysis results are purely coincidental and cannot be traced back to specific influencing factors. If the test confirms the null model, this is not a proof for its correctness. It only leads to a rejection of the hypothesis of the previously assumed dependence on the influencing factors. A null model can not be proven, but only disproved. With suitable methods, so-called surrogates can be created from the original time series (top) or from networks (bottom), whereby the influencing factor to be investigated is hidden and factors to be investigated are masked out. If analysis results for the original data differ from those for a sufficiently large number of surrogates, then the null hypothesis can be rejected with ascertainable certainty. The investigated influencing factor then plays a significant role and must be taken into account when interpreting findings.



The null hypothesis represents the case for which the obtained findings are consequent to the influencing factors and not to the properties of interest of the investigated system. From this null hypothesis, a pertinent model (the so-called null model) is created, and an ensemble of surrogate data is generated by simulating realizations of the model with Monte Carlo methods (Efron, 1982). In these realizations, all relevant statistical and dynamical aspects of the original data are preserved—except the properties which are tested for. If some discriminating statistics of the original data falls outside the expectation range for the surrogate ensemble, the null hypothesis can be rejected with reasonable confidence (depending on the number of statistically independent constrained realizations). In this case, an alternative hypothesis has to be accepted—i.e., findings are likely due to the properties of the system. However, the surrogate approach does not specify alternative hypotheses nor is it a validation of any specific alternative hypothesis' accurateness.

For properties of interactions, constrained realizations of the multivariate time series can be generated by randomizing the aspect of a recorded dynamics on which the estimator for the property of an interaction is based (Schreiber, 1998; Schreiber and Schmitz, 2000; Andrzejak et al., 2003a; Paluš, 2007; Rings et al., 2020). However, the associated surrogate techniques are exclusively designed for the strength of an interaction as the formulation of null hypotheses for the direction of an interaction (linkable to properties of time series for an appropriate null model) continues to be an unsolved problem. The same applies to null hypotheses for the functional form of an interaction.

Having estimated the relevant property of interaction for all pairs of brain regions, the values of the estimates then set up an *interaction matrix* $\mathcal{I} \in \mathbb{R}^{N \times N}$, where $N$ is the number of recorded brain regions.

Subsequently, a binary or weighted and directed or undirected network can be constructed from this matrix.

An *undirected binary network* describes the brain in terms of *connected* or *disconnected* vertices and can be represented by a symmetric adjacency matrix $\mathcal{A} \in \{0,1\}^{N \times N}$ (also referred to as functional connectivity). If two vertices $i$ and $j$ are considered connected, the associated entry $\mathcal{A}_{ij}$ is 1 and 0 otherwise. Typically, two vertices are assumed to be connected, if an estimator for the strength of interaction between the associated brain regions exceeds some threshold. There are, however, no commonly accepted criteria for the selection of the threshold [see, e.g., Kramer et al. (2009); Zanin et al. (2012)]. Alternatively, mesoscopic network structures [e.g., minimum spanning tree (Rammal et al., 1986; Stam et al., 2014) or shell or web decompositions (Bröhl and Lehnertz, 2019; Kong et al., 2019)] can be derived from $\mathcal{I}$ and used as a binary network.

If it is additionally of interest which brain regions interact how strongly, an *undirected weighted network* provides this information. Represented by a symmetric weight matrix $\mathcal{W} \in \mathbb{R}^{N \times N}$ (also referred to as functional connectivity), it is possible to again select a threshold to exclude edges with non-significant strengths of interaction. However, in most cases all edges are considered to exist and form a complete network. Typically, elements of the weight matrix are set to be identical to the elements of the interaction matrix, i.e., $\mathcal{W}_{ij} = \mathcal{I}_{ij}\ \forall\, i, j$.

A *directed binary network* describes the brain by depicting which brain region drives which other region. Extending the concept of undirected binary networks, directed networks can be described by an asymmetric adjacency matrix $\mathcal{D} \in \{0,1\}^{N \times N}$ (also known as effective connectivity), where an entry $\mathcal{D}_{ij}$ is 1, if vertex $i$ is connected to vertex $j$ by a uni-directional edge, and 0 otherwise. If in addition the entry of the inverse direction is also 1 ($\mathcal{D}_{ij} = \mathcal{D}_{ji} = 1$), the vertices are connected by a so-called *bidirectional edge* and are driving each other. A directed edge is assumed to exist, if an indication of direction is strong—e.g., if the value of an estimator for the direction of interaction (or some directionality index derived from the value) exceeds some threshold. Again, the choice of this threshold is arbitrary and there are no commonly accepted criteria for its selection.

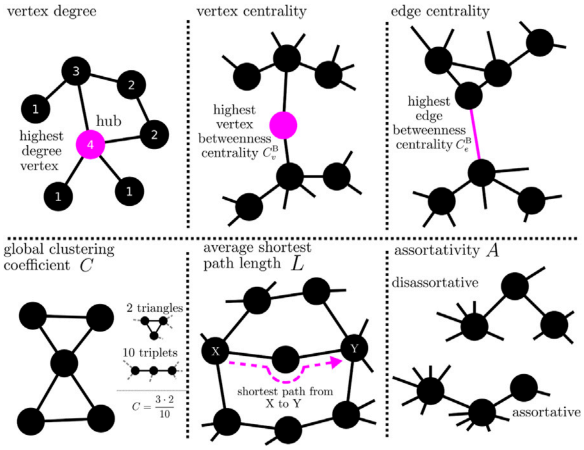
Of note, direction of interaction does not generally inform of strength of interaction, and combining both information in a *directed and weighted network* is a not conclusively solved problem. When merging strength and direction of interaction, it is important to remember that both properties are different but not unrelated (Lehnertz and Dickten, 2015). The often-employed interpretation of the modulus of an estimator for the direction of interaction as strength of interaction might not consistently be accurate and can lead to severe misconceptions—particularly for uncoupled or strongly coupled systems (Osterhage et al., 2007b; Paluš and Vejmelka, 2007; Lehnertz and Dickten, 2015; Günther et al., 2022). It is conceptually unclear how weights should be assigned to forward and backward direction of the edges. Strength of interaction is symmetric under exchange of two vertices, while direction of interaction is not. In addition, many concepts employed to estimate properties of interactions can currently not be mapped to each other. The easiest way to avoid resulting problems is to estimate strength and direction of interaction separately but using methods that are based on the same concepts (e.g., phase synchronization or information flow).

There is also no commonly accepted method to utilize functional forms of interaction to derive networks, and doing so would require an abstract, possibly symbolic assignment of edges. Hypothetically, a system's equations of motion could already be considered a symbolic network were a vertex represents an elementary unit's self-dynamics function and an edge represents a coupling function. However, how to interpret the multitude of possible functions involved as a network's component is highly ambiguous.

## 3.3 Properties of a functional brain network

Having derived a functional brain network from observed data, the next task is to characterize the network's properties and internal organization. While there are a multitude of different network metrics based on concepts and methods from graph theory [see, e.g., Rubinov and Sporns (2010); Newman (2018); Cimini et al. (2019) for an overview; Box 4], they are predominantly defined for undirected (binary or weighted) networks and each metric reflects specific topological or spectral network properties. Network metrics for directed networks are still subject of current research. Two necessary concepts for a characterization of a network are *distance* and *shortest paths*. A *path* is the collection of edges that need to be traversed to reach a constituent starting at another one, and the respective *path length* (which is equivalent to the distance) is either the number of edges that are traversed in case of a binary network, or the sum of the inverse weights of these edges in case of a weighted network. There are multiple paths between every constituents, and shortest paths are the ones whose path lengths are minimal. Generally, network metrics can be categorized according to the network scale for which they are defined—i.e., from the global scale encompassing the whole network to the local scale of single vertices and edges.

BOX 4 Properties of a network can be assessed with different local-to-global network metrics. Local network metrics (top) assess how individual vertices or edges are integrated into the larger network. These metrics can also be used to determine the importance (centrality) of vertices and edges for the network on the basis of objective criteria. For example, a vertex with a high degree (or strength in case of a weighted network) has a strong influence on the network; conversely, the influence of the network on this vertex can be estimated. Betweenness centrality can be used, e.g., to rate the importance of a vertex (or an edge) for the flow of information in a network. Since a vertex (edge) with a high betweenness centrality is traversed by a large number of paths, it acts like a bottleneck in the network. Global network metrics (bottom) evaluate a network as a whole. For example, if the mean value over all local clustering coefficients of a network takes on a high value, then vertices are closely connected to their neighboring vertices (clique formation) In a network whose average shortest path length is large, vertices are only weakly connected with their neighboring vertices; the network tends to break up into different regions. A (dis-)assortative network, vertices tend to connect with other vertices that are (dis-) similar in some way.



## 3.3.1 Global scale

On the global scale, network metrics describe the arrangement of vertices and edges according to topological concepts such as *transitivity* [vertices that are connected to two other vertices that are connected themselves; evaluated with, e.g. (global) clustering coefficient (Watts and Strogatz, 1998)], *efficiency* [information or mass transport in a network is facilitated by short paths; e.g., average shortest path length (Newman, 2001)], or *assortativity* [vertices with the same or similar properties are connected preferentially (Newman, 2002)].

In greater detail, the global clustering coefficient assess the number of closed triplets in relation to the total number of triplets in the network and characterizes a network's functional segregation; segregation decreases with increasing values of the coefficient, however both excessive large or small values indicate a breakdown of segregation. The average shortest path length characterizes a networks functional integration; the shorter the path, the more integrated is the network (cf. Box 5). Assortativity characterizes the mixing of vertices with the similar properties (typically assessed with local network metrics) through being connected (Newman, 2003; Bialonski and Lehnertz, 2013); if edges preferentially connect vertices with a similar (dissimilar) property, such networks are called assortative (disassortative). Disassortative networks are more vulnerable to perturbations and appear to be easier to synchronize than assortative networks (Motter et al., 2005; di Bernardo et al., 2007).

BOX 5 Following Tononi et al. (1994), integration can be defined as an effective global cooperation between different subsystems (brain regions). Segregation can be defined as the decomposition of a system into sufficiently independent specialized processing subsystems.

Additionally, methods from linear algebra can be employed to investigate spectral properties of a network's associated adjacency or weight matrix, which then can be related to a network's emergent global dynamics [for an overview see (Atay et al., 2006; Comellas and Gago, 2007)]. *Synchronizability*, e.g., characterizes the stability of a global synchronization state, i.e., a network's propensity to synchronize (Barahona and Pecora, 2002). However, for an interpretation of synchronizability of human brain networks, one should keep in mind that some of this metric's fundamental assumptions are not fulfilled in this system—for synchronizability, it is assumed that all vertices are associated with dynamics of the same type with largely identical control parameters which strongly disagrees with the spatial heterogeneity of brain dynamics (Papo and Buldú, 2019).

Although it is possible to compensate for this heterogeneity to some degree (while accepting other constraining assumptions) (Sun et al., 2009; Nishikawa and Motter, 2010; Zhang and Motter, 2017), a global synchronization state is fortunately not achieved in the brain (and would indicate complete dysfunction)—an inveterate conceptional issue. Consequently, synchronizability should only ever be treated as an indicator of stability properties of a network's associated dynamics instead of face value.

Global network metrics can also be used to define indices that are thought to be specific to the network's topology. For example, global clustering coefficient and average shortest path are often merged to assess whether a given network has a small-world-like topology or not (Bassett and Bullmore, 2006), and this property has been reported for both structural and functional, physiological and pathophysiological brain networks in the past (Reijneveld et al., 2007; Bullmore and Sporns, 2009; Stam, 2014). These findings, however, are strongly contested (Bialonski et al., 2010; Hlinka et al., 2012; Hilgetag and Goulas, 2016; Papo et al., 2016) due to the identification of various factors that can influence the characterization of networks. Confusingly, the literature frequently refers to various metrics and underlying concepts with different, sometimes overlapping names—e.g., the metric "average shortest path length" and the metric "average communication efficiency" are identical and both are indicators of the conceptual "efficiency" of a network.

### 3.3.2 Local scale

On the local scale, network constituents (vertices as well as edges), can be characterized with so-called centrality metrics. These metrics evaluate a constituent according to the various roles it can play in a network [for an overview see, e.g., Koschützki et al. (2005); Kuhnert et al. (2012); Bröhl and Lehnertz (2019)]. Typically, centrality metrics are based either on the strength with which a constituent is connected to the rest of the network (*strength-based*; e.g., strength centrality or eigenvector centrality) or on their involvement in the organization of shortest paths in a network (*path-based*; e.g., betweenness centrality or closeness centrality). Constituents with high strength-based centrality values are typically considered to affect (and to be affected by) the rest of the network more strongly than constituents with smaller values and are often called *hubs*. Constituents with high path-based centrality values are thought to be important for information or mass transport phenomena on networks, e.g., by being bridges connecting remote network regions (high betweenness centrality) or by reaching other constituents via especially short shortest paths (high closeness centrality).

Local network metrics are also frequently used to assess importance of network constituents by establishing rankings of vertices or of edges (Ghoshal and Barabási, 2011; Lü et al., 2016; Liao et al., 2017). While many studies concentrate on the most important constituents (i.e., the vertex or edge with the highest centrality value), information from the full spectrum of centrality values can be educational when considering the network's complete internal organization.

### 3.3.3 Intermediate scale

Extensions of network metrics to an intermediate, mesoscopic scale are subject of current research. In principle, sub-networks can be identified via, e.g., community or module detection (Fortunato and Hric, 2016) or shell or web decompositions (Bröhl and Lehnertz, 2019; Kong et al., 2019) on this scale and then characterized with global or local metrics instead of the whole networks. However, most sub-network identification schemes are themselves based on local network metrics, which might lead to an overemphasis on the concept behind the used local metric. Also, the interpretation of such a characterization of sub-networks is hitherto unclear. Alternatively, the relative amounts of so-called graphlets or motifs (smallest sub-networks interpreted as generic building blocks) can be investigated and related to theoretical arguments about the roles of these objects in a network (Newman, 2006; Alon, 2007; Ribeiro et al., 2021).

In principle, estimating network metrics can be affected by the same adverse influences that also affect the estimation of properties of interactions—either by error propagation or by influencing a researcher's decision about how to derive the network based on preliminary results (e.g., a higher average strength of interaction might bias the decided-on level of a threshold for a binary network). Especially, oversampling (effectively recording the same dynamics multiple times) and common sources (due to, e.g., referential recording) can lead to misinterpretations (Porz et al., 2014) since especially estimators for strength of interaction identify largely identical time series as an indication of very strong interactions, which in turn influence, e.g., strength-based centrality metrics. In addition, statistical uncertainties from the estimation of properties of interactions can be amplified in unexpected ways when they are merged into network metrics. In some of these cases, so-called *network surrogates* (cf. Box 3) can be employed to improve reliability and reduce adverse influences (Ansmann and Lehnertz, 2011; 2012; Wiedermann et al., 2016; Stahn and Lehnertz, 2017; Váša and Mišić, 2022). These surrogates are constrained realizations of the investigated network by randomizing edges (or their weights) while preserving selected network properties such as network size, density of edges, or distribution of edge weights. Then, to decide to which extent a metric of a given network is determined by these properties, its value can be compared to the values for surrogates of this network. Associated null hypotheses typically state that the internal network organization assessed by the network metric is random under the constraint of the preserved properties.

Finally, to trace time-dependent changes of a network and its internal organization over time, networks are derived for each of the above-mentioned segments of time series of recordings of brain dynamics. This results in a sequence of snapshot networks—the time-evolving functional brain network—and time series of the various network metrics, which can be again investigated with methods from time series analysis (cf. Figure 1).

## 3.4 Characterizing a time-evolving brain network

In the previous subsection, we critically assessed the construction of a (snapshot) functional brain network from windowed data of observed brain dynamics (such as EEG, MEG, or fMRI) using bivariate time-series-analysis techniques and the characterization of this network using graph-theoretical concepts and methods. Performing such analyses for successive windows of observed data results in a temporal sequence of snapshot functional brain networks together with time series of the networks' metrics, both at a temporal resolution that results from the duration of an analysis window. The sequence and the respective time series form the basis for in-depth studies of a time-evolving brain network which can potentially provide more detailed information about the network's temporal fluctuations and its complex interplay with ongoing physiologic activities compared to what can be achieved with snippets of recordings of brain dynamics that usually last only a few tens of seconds. Among others, the temporal fluctuations can inform about the significance of averaged quantities such as mean values of some network metrics (Lehnertz et al., 2017; 2021) that are widely used in the network neurosciences.

The identification of spontaneous or induced (patho-)physiologic changes within a sequence of snapshot networks requires estimating some *distance* or (dis-)similarity between two (not necessarily successive) networks (or adjacency matrices). Finding suitable metrics for such a comparison, however, continues to be a difficult task (Bronstein et al., 2006; Andrade et al., 2008; Muskulus et al., 2009; Dimitriadis et al., 2010; Gao et al., 2010; van Wijk et al., 2010; Mémoli, 2011; De Domenico and Biamonte, 2016; Schieber et al., 2017; Fraiman and Fraiman, 2018; Carpi et al., 2019; Martínez and Chavez, 2019; Hartle et al., 2020; Mheich et al., 2020; Lacasa et al., 2021). Difficulties might even aggravate if network size (number of vertices) and edge density depend on time.

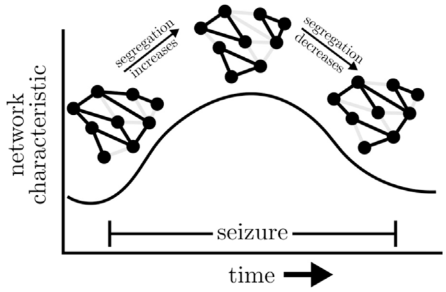
An alternative approach is offered by the investigation of time series of the networks' metrics employing the powerful spectrum of methods from (linear/nonlinear) uni-, bi-, or multivariate time-series-analysis (Bendat and Piersol, 1980; Haykin, 1983; Pikovsky et al., 2001; Kantz and Schreiber, 2003; Reinsel, 2003; Lütkepohl, 2005; Wen and Cheong, 2021; Caligiuri et al., 2023). Statistical (Efron, 1982; Basseville and Nikiforov et al., 1993; Anderson, 2011) as well as Fourier and related analyses (Press and Rybicki, 1989; Huang et al., 1998; Percival and Walden, 2000; Kantelhardt et al., 2001; Bloomfield, 2004) can help to detect anomalies and change points (Aminikhanghahi and Cook, 2017) as well as to assess correlations and periodicities (for an example, see Figure 2). Bi- and multivariate analyses facilitate identification of relationships and interdependencies between time series of different networks' metrics assessed on the various network scales—from single constituents via communities to the wider network. Before closing this section, we briefly mention another, but so far insufficiently studied analysis approach to investigate time-evolving functional brain networks. It is based on the concept of a multilayer network (Boccaletti et al., 2014; Kivelä et al., 2014; Presigny and Fallani, 2022), which is a complex network structure that consists of multiple networks (e.g., a sequence of snapshot networks). Despite a continuous development of metrics to characterize such a network of networks (Battiston et al., 2014; De Domenico et al., 2015; Nicosia and Latora, 2015; Iacovacci and Bianconi, 2016; Ghariblou et al., 2017; Mandke et al., 2018; Tudisco et al., 2018; Zaoli et al., 2021), applications in the neurosciences and related fields mostly center around frequency-based decompositions or structural and functional decomposition (De Domenico, 2017; Buldú and Porter, 2018; Vaiana and Muldoon, 2020). Due to a number of fundamental problems that arise with this approach, a meaningful interpretation of multilayer brain networks is still to be explored (Buldú and Papo, 2018; Mandke et al., 2018).

## 4 The time-evolving epileptic brain network: What have we learned so far?

### 4.1 The time-evolving epileptic brain network during seizures

Various studies reported increased global clustering coefficients and—although to a lesser extent—average shortest path lengths of time-evolving epileptic brain networks during focal and primary generalized seizures [see, e.g. (Ponten et al., 2007; Kramer et al., 2008; Schindler et al., 2008; Ponten et al., 2009; Kramer et al., 2010)] compared to the seconds before or after a seizure. For 100 focal seizures from 60 people with epilepsy, this observation could be made irrespective of their anatomical onset location (Schindler et al., 2008). If investigated with high temporal resolution (Schindler et al., 2008; Kramer et al., 2010), both network metrics exhibited a concave-like temporal evolution which points to a movement from a more random toward a more regular and more segregated and then back toward a more random functional topology of the epileptic brain network (cf. Box 6). A similar evolution was also observed for time-evolving epileptic brain networks during status epilepticus (Kuhnert et al., 2010).

**BOX 6 Schematic change of exemplary global network metric (here: global clustering coefficient and average shortest path length) and changes of the functional topology during seizure.**



Some authors (Ponten et al., 2007; Kramer et al., 2008; 2010) interpreted the evolution to reflect the small-world topology of short paths and high clustering (Watts and Strogatz, 1998), which is thought to support efficient communication between brain regions at the lowest energetic cost under physiological and pathophysiological conditions (Bassett and Bullmore, 2006; Reijneveld et al., 2007; Bullmore and Sporns, 2012; Stam, 2014). The validity of such an interpretation, however, continues to be matter of considerable debate (Bialonski et al., 2010; Gerhard et al., 2011; Hlinka et al., 2012; Hilgetag and Goulas, 2016; Papo et al., 2016; Hlinka et al., 2017; Zanin et al., 2018) given a large number of factors that have been identified to impact on global clustering coefficient and average shortest path length.

For the same 100 focal seizures from 60 people with epilepsy mentioned above, Bialonski and Lehnertz (2013) reported on a concave-like temporal evolution of assortativity, with a more assortative topology during seizures than during the seconds before or after a seizure. Interestingly, assortativity decreased already prior to seizure end. An increasing assortativity indicates a division of the evolving epileptic brain network into groups of brain regions that are only sparsely interconnected, if at all. Such networks have a comparatively resilient core of mutually interconnected high-degree vertices as has been observed by Zubler et al. (2015) for 198 seizures from 27 people with epilepsy. This core makes epileptic brain networks during seizures quite robust against perturbations, which might explain the mixed success of active brain stimulation to interrupt seizures (Morrell, 2006; Hirsch and Schulze-Bonhage, 2023).

It is important to note that the aforementioned topological network alterations are not accompanied by an increased network synchronization [see, e.g., Schindler et al. (2007b; a); Cash (2013); Majumdar et al. (2014)], which puts into

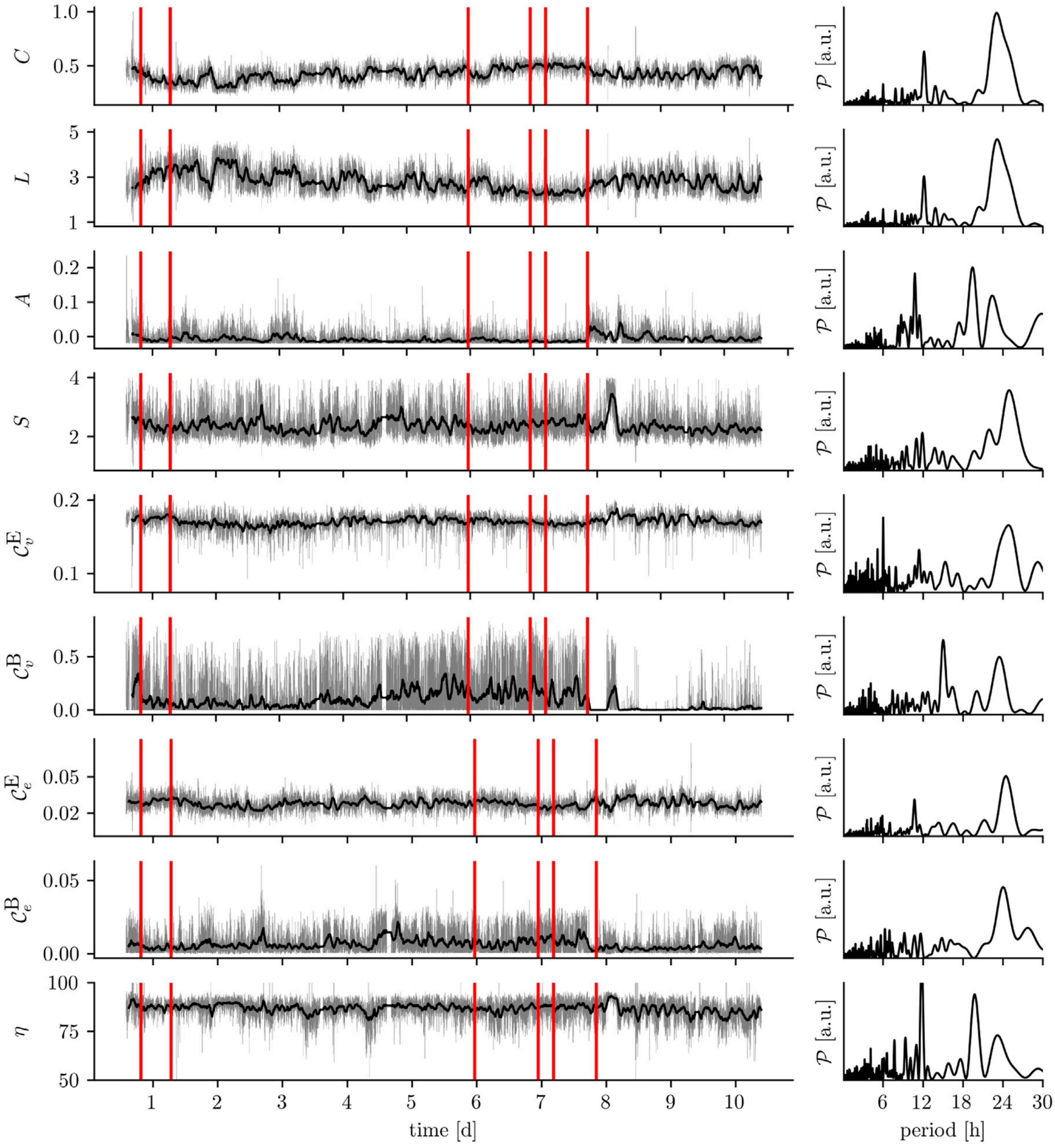


FIGURE 2
Exemplary time series of various network metrics: global clustering coefficient $C$, average shortest path length $L$, assortativity $A$, synchronizability $S$, eigenvector centrality $\mathcal{C}^{\mathrm{E}}_{\mathrm{v,e}}$ and betweenness centrality $\mathcal{C}^{\mathrm{B}}_{\mathrm{v,e}}$ for vertices (v) and edges (e) being most central, on average, and relative number of edges in most important web $\eta$ (Bröhl and Lehnertz, 2019). Time series derived from a multichannel ($N = 52$), long-term (9.8 d) intracranial EEG recording from a subject with a focal epilepsy undergoing presurgical evaluation (the subject signed informed consent that the clinical data might be used and published for research purposes, and the study protocol had previously been approved the by ethics committee of the University of Bonn). Left column shows full (grey) and smoothed time series [black, moving average over 176 windows (1 h) to improve legibility], and tics on x-axis denote midnight. Red lines mark onset of epileptic seizures. Right column shows power spectral density estimates [Lomb–Scargle periodograms (Press and Rybicki, 1989)] of the unsmoothed time series.

perspective the textbook description of seizures as hypersynchronous events (see also Jiruska et al., 2013). Rather, studies on network synchronization and on the networks' synchronizability indicate that the changing network topology during seizures is accompanied by an initially decreased network synchronization and decreased stability of the globally synchronized state, both of which increase already prior to seizure end (Schindler et al., 2008; Kramer et al., 2010; Khambhati et al., 2015; Frassineti et al., 2021; Rungratsameetaweemana et al., 2022; Salami et al., 2022). These synchronization phenomena may thus be considered as an emergent (network-topology-mediated) self-regulatory mechanism for seizure termination (Lado and Moshé, 2008; Kramer et al., 2012). It is also important to note that the seizure-related topological network alterations are similar across different types of epilepsies, seizures, medication, age, gender, and other clinical features (see also Haneef and Chiang, 2014). This might point to a common mechanism underlying seizure dynamics in the epileptic brain network (Lehnertz et al., 2014).

In addition to these global aspects of time-evolving epileptic brain networks, several studies investigated the role that network vertices and edges play in seizure evolution (Kramer et al., 2008; Wilke et al., 2011; Varotto et al., 2012; Burns et al., 2014; Geier et al., 2015a; Zubler et al., 2015; Goodfellow et al., 2016; Geier and Lehnertz, 2017b; Bröhl and Lehnertz, 2019; Bröhl and Lehnertz, 2022). Employing various centrality and other metrics to characterize a constituent's importance for seizure dynamics, most studies reported these metrics to exhibit a high temporal variability as seizures evolve, both inter- and intraindividually. While some studies reported most important vertices (if based on a metric's temporal mean) to coincide with the clinically defined seizure onset zone (SOZ), other studies could not confirm such a relationship. Rather, network vertices associated with brain regions deemed unaffected by the pathology and more recently also edges (Bröhl and Lehnertz, 2019; Bröhl and Lehnertz, 2022) that functionally connect these vertices were reported as most important during the course of a seizure. If at all, vertices that can be associated with the SOZ gained importance towards the end of a seizure (Burns et al., 2014; Geier et al., 2015a; Zubler et al., 2015).

It remains to be investigated which factors could have led to these inconsistencies, apart from methodological issues (Geier and Lehnertz, 2017b). Nevertheless, the observation of network constituents that are most important during seizures but appear to be unrelated to pathological brain tissue not only underlines the significance of the concept of an epileptic network but also puts into perspective the role of the epileptic focus in seizure dynamics (see also Paz and Huguenard, 2015). One might speculate whether such network constituents represent potential targets for focused therapeutic interventions.

## 4.2 The time-evolving epileptic brain network during the pre-seizure state

Despite the well-known observation that *vulnerability to seizure activity in any one part of the network is influenced by activity everywhere else in the network, and that the network as a whole is responsible for the clinical and electrographic phenomena that we associate with human seizures* (Spencer, 2002), we still lack a sufficient quantitative assessment of the time-evolving epileptic brain network's metrics (from the local to the global network scale) that would help to improve understanding of how the network generates seizures (Kuhlmann et al., 2018; Lehnertz, 2021; Lehnertz et al., 2023) as well as other pathophysiological phenomena (Weiss et al., 2022).

Nevertheless, first indications for certain network reconfigurations to promote the formation of a pre-seizure state could be derived from retrospective studies that investigated macroscopic metrics of time-evolving epileptic brain networks. Kuhnert et al. (2010) analyzed more than 2,100 h of continuous intracranial EEG recordings from 13 subjects with epilepsy during which 75 focal onset seizures and one status epilepticus occurred. From the time series of global clustering coefficients and average shortest path lengths, the authors observed the distributions of these metrics from pre-ictal periods [assumed duration: 4 h; cf. Mormann et al. (2006)] to significantly deviate from the respective distributions of metrics derived from inter-ictal data. Both these global metrics of network structure attained higher values (on average) pre-ictally in the majority of subjects, which the authors interpreted as indications for a loss of functional long-range connections during the pre-ictal period. Geier et al. (2015b) performed similar analysis for assortativity (here: degree-degree correlations) based on more than 1,000 h of continuous intracranial EEG recordings from seven subjects with epilepsy during which 16 focal onset seizures occurred. Pre-ictally, a slightly less assortative mixing of time-evolving epileptic brain networks was observed, which might indicate these networks to be less robust against (endogenous and/or exogenous) perturbations. Both, Kuhnert et al. (2010) and Geier et al. (2015b) stressed, however, the strong influence of daily rhythms seen in the time series of the investigated network metrics (cf. Section 4.3) that would need to be taken into account to avoid misinterpretations (see also Takahashi et al., 2012).

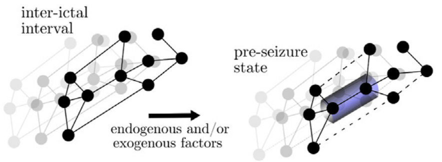
More recently, Rings et al. (2019a) used the network approach to develop a time-series-analysis technique that allows tracing resilience of a networked dynamical system (Fischer et al., 2022), such as the brain. The authors investigated more than 3,200 h of continuous intracranial EEG recordings from 43 subjects with epilepsy during which 112 focal onset seizures occurred. They observed the distribution of the network resilience estimator (dynamical resistance) from 4 h pre-ictal periods to significantly deviate from the respective distribution of the metric derived from inter-ictal data. The achieved high, above-chance-level predictive performance [evaluated with seizure time surrogates (Andrzejak et al., 2003b)] of dynamical resistance would qualify this resilience estimator for seizure-prediction studies. In passing, we note that other estimators of resilience such as those related to the concept of critical slowing down failed to achieve a sufficient predictive performance (Milanowski and Suffczynski, 2016; Wilkat et al., 2019; Hagemann et al., 2021) rating this concept overly simplistic for the human epileptic brain. Interestingly, dynamical resistance increased in the hours prior to the vast majority of seizures. Although one would expect intuitively resilience to decrease in order to facilitate the generation of a seizure, the authors speculated that the reduced effectiveness of antiseizure medication may account for the observed increase. One might also speculate [see the discussions in Frei et al. (2010); Zaveri et al. (2020)] that a pre-ictally increased brain resilience could also reflect the epileptic brain network's ability to efficiently defy control because of its intrinsic plasticity and adaptiveness. In this context, epilepsy may be viewed as a "learned" disease and seizures as an abnormal learned response to recurrent perturbations—such as seizures (Turrigiano, 1999; Hsu et al., 2008; Lignani et al., 2020; Issa et al., 2023).

In addition to studies on pre-seizure-state-related alterations of functional segregation and integration as well as of robustness of the time-evolving epileptic brain network, further in-depth insights into pre-seizure network reconfigurations could be achieved with investigations of time-dependent changes of properties of the network's vertices and edges. Tauste Campo et al. (2018) investigated non-continuous intracranial EEG recordings from 10 subjects with epilepsy and used an averaged vertex eigenvector centrality to characterize network state variability. The authors observed network states to become less variable a few hours preceding a global functional connectivity reduction before seizure onset [cf. Mormann et al. (2000; 2003); Kuhlmann et al. (2010); Lehnertz et al. (2016)].

Analyzing retrospectively more than 3,200 h of continuous intracranial EEG recordings from 38 subjects with epilepsy during which 97 focal onset seizures occurred, Rings et al. (2019b) observed distributions of vertex centrality (strength and betweenness centrality) and edge weight from 4 h pre-ictal periods to significantly deviate from the respective distributions of these local network metrics derived from inter-ictal data. The authors reported high, above chance level predictive performance for these deviations and observed that most brain regions (vertices) whose dynamics carried predictive information were connected by most of the edges whose time-dependent weight changes carried predictive information. These vertices, however, never played a central role in the investigated time-evolving epileptic brain networks. More importantly, these vertices were entirely associated with brain regions far off the clinically defined SOZ.

Based on these observations, the authors proposed a scenario for the generation of seizure precursors in a time-evolving epileptic brain network (cf. Box 7): endogenous and/or exogenous factors trigger a rearrangement of the network's path structure which eventually leads to a formation of bottlenecks in brain regions deemed unaffected by the pathological process which in turn impairs physiologic brain communication [cf. (Avena-Koenigsberger et al., 2018)]. These brain regions, being part of the large-scale epileptic brain network, generate and sustain normal, physiologic brain dynamics during the inter-ictal intervals. Moreover, they also appear to efficiently control the dynamics of vertices related to the SOZ (Lehnertz and Dickten, 2015; Dickten et al., 2016; Johnson et al., 2023).

BOX 7 The path-structure (i.e., layout of the paths in the network) of the functional network is altered prior to seizure, culminating in the forming of bottlenecks. Black networks represent the average functional network in the respective interval. Dotted edges indicate lower interaction strength.



Fruengel et al. (2020) investigated retrospectively continuous intracranial EEG recordings that were part of previous studies (Lehnertz et al., 2016; Rings et al., 2019b) and employed different strength- and path-based vertex centrality metrics (strength, eigenvector, closeness and betweenness centrality) to further improve understanding of local and global reconfigurations of the time-evolving epileptic brain network during the pre-seizure period. The authors observed distributions of vertex centrality from 4 h pre-ictal periods preceding 99 seizures to significantly deviate from the respective distributions of these local network metrics derived from inter-ictal data. As a result of high, above chance level predictive performances for these deviations in various brain regions, they proposed several major scenarios for a pre-seizure reconfiguration of the time-evolving epileptic brain network. With these scenarios, pre-seizure changes in the network are not necessarily confined to specific brain regions. Rather, local and global reconfigurations of the time-evolving epileptic brain network appear to affect virtually all network constituents, i.e., various vertices (brain regions) and the edges (functional connections) between them. Focusing on the pre-seizure changes in degree and betweenness centrality of vertices associated with the SOZ, Sumsky and Greenfield Jr (2022) recently reported similar findings in the seconds prior to 143 seizures from 20 subjects with epilepsy and investigating a comparable amount of continuous intracranial EEG recordings (more than 3,300 h).

## 4.3 The time-evolving epileptic brain network during seizure-free intervals

If a time-evolving epileptic (and non-epileptic) brain network is derived from continuous multiday, intracranial or scalp-recorded EEG, virtually all time series of the network's metrics—from local to global—exhibit large fluctuations over time which appear to be partly periodic (cf. Figure 2). These periodicities can be correlated with the circadian and various ultradian rhythms (Kuhnert et al., 2010; Takahashi et al., 2012; Lehnertz et al., 2014; Geier et al., 2015b; Geier and Lehnertz, 2017a; Lehnertz et al., 2017; Rings et al., 2019a; Chiosa et al., 2019; Mitsis et al., 2020; Healy et al., 2021; Lehnertz et al., 2021; Bröhl et al., 2023), which are also thought to modulate seizure risk (Bernard, 2021; Karoly et al., 2021) and seizure dynamics (Schroeder et al., 2020). Despite these large periodic fluctuations, additional alterations of network metrics can be observed on shorter time scales (some tens of seconds to few minutes) typically covered in clinical and research studies. These (mostly time-averaged) alterations of metrics seen in epileptic brains clearly differ from those seen in healthy ones (Chavez et al., 2010; Horstmann et al., 2010; Vlooswijk et al., 2011; Zhang et al., 2011; Richardson, 2012; Caciagli et al., 2014; Haneef and Chiang, 2014; Stam, 2014; Chiang et al., 2015; Foit et al., 2020; Pegg et al., 2020; Slinger et al., 2022). Importantly, they also differ between different types of epilepsy (Lee et al., 2006; Barzegaran et al., 2012; Bartolomei et al., 2013; Chowdhury et al., 2014; van Diessen et al., 2016; Rosch et al., 2018; Kinney-Lang et al., 2019; Lopes et al., 2019; Marino et al., 2019; Ahmadi et al., 2020; Pegg et al., 2020; Woldman et al., 2020; Pegg et al., 2021; Slinger et al., 2022; Tufa et al., 2022). Identifying alterations of network metrics is thus thought to contribute to improving differential diagnosis, treatment, surgical planning, and estimation of prognosis.

This perspective is further supported by research findings of alterations of network metrics due to factors that are known to modulate the epileptic process such as cognition (Kuhnert et al., 2013; Shine, 2019), treatment with antiseizure medication (Anderson et al., 2020; Hatlestad-Hall et al., 2021) and with neuromodulation such as deep brain stimulation (Khaledi-Nasab et al., 2022; Vetkas et al., 2022), responsive neurostimulation (Piper et al., 2022), and vagus nerve stimulation (VNS) (Fraschini et al., 2014). As regards the latter, investigations in larger groups of subjects with epilepsy and in healthy controls (Rings et al., 2021; von Wrede et al., 2021; 2022a;

b) demonstrated that short-term, non-invasive transcutaneous auricular VNS can induce small but measurable immediate and enduring alterations of global metrics of the time-evolving epileptic brain network while leaving its local metrics essentially unchanged. The differential alterations of local and global network metrics can be understood using the model of stimulation-mediated stretching and compression of the time-evolving epileptic brain network proposed by Rings et al. (2021). This model takes into account the changes of the network's path structure (average shortest path length) and of its tendency to form tightly knit groups of vertices (global clustering coefficient) as well as the centrality (importance) hierarchies of vertices and edges to characterize stimulation-mediated modifications of the larger network. The authors conjectured that these topology-modifying stretching and compression effects likewise impact on the network's assortativity and synchronizability, thereby enhancing its robustness and stability.

Recently, Lehnertz et al. (2023a) reported on a similar reconfiguration and modification of networks together with their stability and robustness properties in a group of 20 subjects with and without epilepsy upon a short-term manual visceral-osteopathic stimulation of the vagus nerve at the abdomen. This finding may add to the current discussion on the importance of the gut-brain axis in the treatment of epilepsy (Ding et al., 2021; Sinha et al., 2022) and to further enhance our understanding of how multiple organs in the human body dynamically interact as a network and integrate their functions to generate (patho-)physiological states (Ivanov, 2021).

## 4.4 A model for the temporal evolution of the epileptic brain network

Summarizing the findings achieved so far, we propose a model for the temporal evolution of the epileptic brain network (cf. Figure 3A). To this end, we consider an abstract "phase-space" that is spanned by the networks' global clustering coefficients $C$, average shortest path lengths $L$, and synchronizabilities $S$ to capture the diurnal variation of segregation, integration, and the networks' propensity to synchronize (although they are correlated, we use $C$ and $L$ to facilitate readability). The networks' motion in this space is largely dominated by the circadian rhythm (with a period length of about 24 h; cf. Figure 2), with a comparably lower (higher) segregation (integration) as well as an increased propensity to synchronize during daytimes. This global motion is modulated by ultradian rhythms with period lengths around 12 h and shorter, seen during both night- and daytimes (cf. Figure 2). These modulations likely reflect different sleep/vigilance states and their accompanying modifications of critical network properties [such as segregation and integration (Deco et al., 2015) as well as the propensity (or vulnerability) to be synchronized by an admissible input activation] may account for the well-known fluctuations of epileptic activities and seizure occurrence (Spencer et al., 2016; Khan et al., 2018). Interestingly, the networks' motion is, in general, only sparsely modulated by comparably short-lasting exogenous (e.g., neurostimulation; cf. Section 4.3 and Figure 3B) and endogenous perturbations (seizures; cf. Section 4.1 and Figure 3C). Nevertheless, the specific manner of these modulations provides novel insights into the effectiveness of neurostimulation/-modulation approaches as well as into network mechanisms of pre-seizure dynamics (cf. Section 4.2), seizure generation, spread, and termination.

# 5 Current limitations and potential prospects

Initiated by Susan Spencer's seminal work on neural networks in human epilepsy, the last two decades have seen quite a number of accomplishments in defining and characterizing the epileptic brain network, including an important change in perspective from a static to a time-evolving network (cf. Li et al., 2017), which better takes into account the fact that epilepsy is a dynamic disease. Nevertheless, much remains to be completed in the coming years, and several issues need to be addressed to advance the field.

## 5.1 Methodological issues

Beginning with collecting the brain's structure and dynamics, there is a strong need for a recording technique that allows one to capture the multiple spatial and temporal scales of the epileptic process. If different recording techniques are used, there is still the problem of an unambiguous fusion of the different scales (Schevon et al., 2019; Driscoll et al., 2021; Presigny and Fallani, 2022). Likewise, suitable strategies to avoid spatial and temporal oversampling of brain dynamics are urgently needed since oversampling can lead to severe misinterpretations of network characteristics (Bialonski et al., 2010; Zalesky et al., 2010; Bialonski et al., 2011; Joudaki et al., 2012; Montes-Restrepo et al., 2014; Porz et al., 2014; Puce and Hämäläinen, 2017; Conrad et al., 2020; Vorderwülbecke et al., 2020; Iivanainen et al., 2021; Allouch et al., 2023). It remains to be shown whether recent developments of edge/vertex removal strategies (Bellingeri et al., 2020; Bröhl and Lehnertz, 2023) [or, in case of undersampling, techniques to predict edges (Zhou, 2021) and to detect hidden vertices (Su et al., 2012)] can help to avoid misinterpreting characteristics of the time-evolving epileptic brain network.

Open questions related to deriving functional brain networks from recordings of brain dynamics were recently summarized by Korhonen et al. (2021). Beyond that, we note that defining network edges from properties of an interaction between pairs of brain regions derived from their dynamics is predominantly based on bivariate time-series-analysis techniques that assume a deterministic mechanism behind interactions and any stochastic aspect is treated as mere measurement noise. Recent developments in characterizing two-dimensional stochastic processes (Rydin Gorjão et al., 2019; Aslim et al., 2021) based on the Kramers–Moyal expansion might provide novel insights into stochastic interactions in the future. Likewise, a further improved characterization of the temporal structure of the brain's dynamics could be achieved with bivariate ordinal time-series-analysis techniques (Lehnertz, 2023) that allow one to assess both strength and direction of an interaction. Moreover, while there is an increasing interest in so-called higher-order

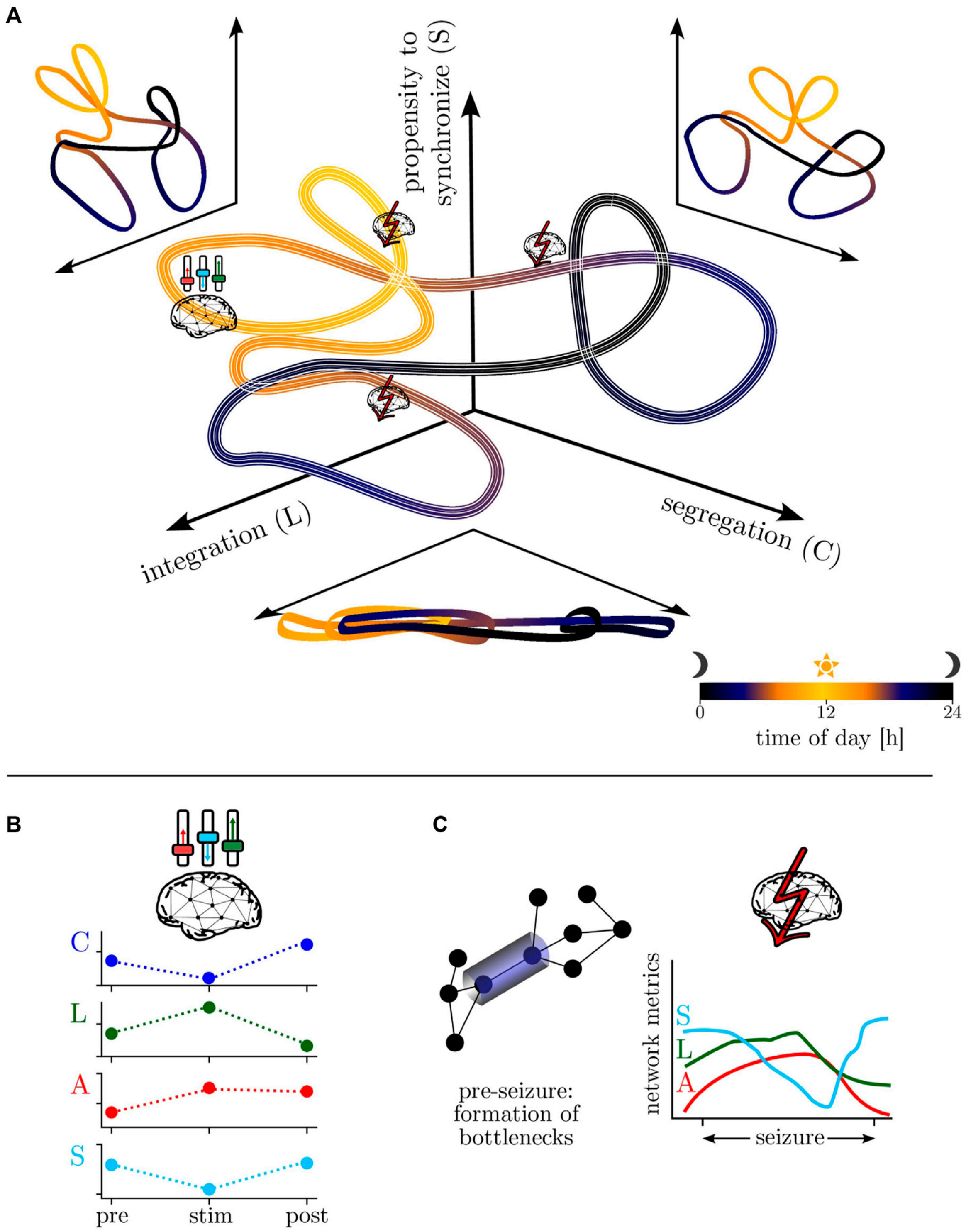


FIGURE 3
**(A)** Model of the temporal evolution of the epileptic brain network in an abstract "phase-space"—spanned by the networks' properties of segregation, integration, and propensity to synchronize—over the day-night cycle (color-coded). Line thickness encodes infradian variability. **(B)** Schematic of neurostimulation-induced modifications of global network properties (global clustering coefficient *C*, average shortest path length *L*, assortativity *A*, synchronizability *S*; local ones remain essentially unchanged). **(C)** Schematic of local network modifications (here: formation of bottlenecks) related to pre-seizure dynamics and of global modifications related to seizure dynamics.

interactions (Battiston et al., 2021; Bianconi, 2021; Boccaletti et al., 2023) (interactions between more than pairs of brain regions), it remains unclear how to estimate the relevant higher-order interactions from time-series data and what advantages such *hyper networks* will provide aside from theoretical arguments.

In Sections 3.3 and 3.4, we presented network metrics and analysis tools to characterize a time-evolving brain network and briefly discussed their pros and cons. Most concepts and metrics were initially developed to characterize static networks and are not immediately transferable to a time-evolving network. Recently proposed analysis tools for time-dependent networks [see, e.g., De Domenico (2017); Thompson et al. (2017); Salcedo-Sanz et al. (2022)] are either not straightforward to convert to weighted and complete networks (as in case of EEG-derived functional brain networks) or wait for proof of their suitability for characterizing a time-evolving epileptic brain network. In general, concepts and metrics proposed and used to characterize static networks need to be redefined or appropriately extended to time-evolving networks, also to account for the impact of time ordering on causal relationships in weighted and directed networks.

Additional in-depth insights into the complex behavior of a time-evolving epileptic brain network prior to and during seizures could be achieved with novel concepts and tools to characterize signal propagation in complex networks (Hens et al., 2019; Ji et al., 2023) and synchronized dynamics of time-varying networks (Ghosh et al., 2022). Considering the recent promising developments of centrality concepts and metrics to characterize properties of edges as well as the edges' time-varying role in the larger network (Bröhl and Lehnertz, 2019; Bröhl and Lehnertz, 2022; Contisciani et al., 2022; Altafini et al., 2023), adopting an edge-centric perspective (cf. Faskowitz et al., 2022; Novelli and Razi, 2022) could lead to a further improved understanding of the time-evolving epileptic brain network and its control (Sinha et al., 2022; Lehnertz et al., 2023; Frauscher et al., 2023).

## 5.2 Conceptual issues

A variety of computational/mathematical models for epilepsy have been proposed [see, e.g., Lytton (2008); Holt and Netoff (2013); Depannemaecker et al. (2021); Pathak et al. (2022)], mostly based on concepts from dynamical systems theory. The majority of these models focuses on seizure dynamics (initiation, spread, termination) only, and the network character of the disease is only rarely taken into account (Kalitzin et al., 2019; Goodfellow et al., 2022). Seizure-like events (states of synchronous rhythmic activity), however, may also emerge spontaneously—i.e., without a change in control parameters—from an oscillator network with some balance between regular and random topology (Rothkegel and Lehnertz, 2014; Ansmann et al., 2016; Gerster et al., 2020; Anesiadis and Provata, 2022; Wu et al., 2022). Other mechanisms behind tipping phenomena include noise-, rate-, and shock-induced tipping [see, e.g., Ashwin et al. (2012); Feudel et al. (2018); Ritchie et al. (2023); Swierczek-Jereczek et al. (2023)]. A better understanding of how seizures emerge from an aberrant, time-evolving epileptic brain network would profit from considering, e.g., critical transition scenarios other than bifurcation-induced tipping which may be too simplistic for the human epileptic brain (Wilkat et al., 2019). Neither of these phenomena require any change of the system's stability, and various time-series-analysis techniques have been proposed to identify early warning indicators (George et al., 2021; Heßler and Kamps, 2022).

Similarly, a better understanding of the longer time scales of brain dynamics that govern the recurrence of seizures would profit from considering mechanisms that can give rise to various long term, fluctuating behavior. We here mention switching phenomena related to the different types of intermittency (Perez Velazquez et al., 1999; Rizzi et al., 2016; Pisarchik et al., 2018), switching in fast-slow systems (Kuehn, 2011) and in heteroclinic networks (Kirst and Timme, 2008; Aguiar et al., 2011; Bick and Field, 2017; Morrison and Young, 2022; Meyer-Ortmanns, 2023) multistability (Lopes da Silva et al., 2003; Takeshita et al., 2007; Rothkegel and Lehnertz, 2009; Breakspear, 2017; Pisarchik and Hramov, 2022), and metastability (Kelso, 2012; Tognoli and Kelso, 2014; Rossi et al., 2023). The validity of such models could be tested if continuous long-term recordings of brain dynamics—covering weeks to months [see, e.g., Weisdorf et al. (2019); Duun-Henriksen et al. (2020)]—would be publically available.

## 5.3 Translational issues

In order to consolidate the network approach into clinical practice, the following issues would need to be tackled.

*Diagnosing epilepsy:* The understanding and treatment of epilepsy requires a clear-cut diagnosis of the possibly underlying disease, allocation of syndromes, and distinction from other neurological and non-neurological diseases, in comparison to a healthy brain. Nevertheless, the techniques currently used routinely only allow a clear-cut diagnosis in, on average, 50% of the subjects (Oto, 2017; Elger and Hoppe, 2018; Amin and Benbadis, 2019), which can probably be related to a number of confounding factors. It can be conjectured that the incorporation of the concept of a time-evolving epileptic brain network into aforementioned differentiation steps can lead to an improved diagnosing and classification of epilepsy, even on a personalized level (Nabbout and Kuchenbuch, 2020).

*Choosing treatment:* Currently, clinical decisions regarding treatment options are primarily guided by the epilepsy syndrome and its burden. Despite several options [e.g., pharmacological treatment (Kwan and Brodie, 2000; Wandschneider and Koepp, 2016; Höller et al., 2018; Höller and Nardone, 2021), surgical treatment (Téllez-Zenteno et al., 2007), nutritional treatment (Pizzo et al., 2022), neurostimulation (Schulze-Bonhage, 2019; Piper et al., 2022); see Lehnertz et al. (2023) for an overview of network-based treatment concepts], the treatment is successful in only about half of the cases. Moreover, from a clinical point of view, the goal of epilepsy treatment is seizure freedom and if this is not possible reduction of seizure frequency and burden of the disease. However, the epileptic brain is not a temporarily disturbed normal brain, and a seizure is not a clinical sign of a transient dysfunction of a normal brain. Therefore, on a conceptual level, the treatment of epilepsy should be addressed more as the treatment of an evolving epileptic brain rather than treating seizures. Further investigation into the network-modulating effects of different interventions—adopted to the time-evolving epileptic brain network—is vital to provide physicians with information about the best and most promising treatment options in individual treatment situations.

*Optimizing and monitoring therapy:* Treating subjects with epilepsy means to achieve a situation in which the subject not only has no seizures, despite the disease epilepsy, but also is able to live an unimpaired life. Impairments result not only from seizures, but also possibly from an underlying structural correlate, and the epilepsy treatment. A thorough clinical action includes therapy monitoring, adapting therapies to the current situation, and preferably acting with foresight in order to avoid anticipatory therapy consequences. However, available data is limited by the subjective perception and possible inadequate sampling of other influencing dynamics and their interactions [e.g., pharmacokinetics, biological rhythms, fluctuations of the endocrinal system (Lehnertz et al., 2020; Healy et al., 2021)], and hence is not yet sufficient to reliably inform such clinical action. Individual tracking the epileptic brain's network changes over the time—not only during seizures, but also in response to chronic treatment, during everyday activities and therapeutic *ad hoc* interventions—are needed, to unveil the potential for tailored epilepsy treatment. This treatment should be targeted at the time-evolving epileptic brain network and keep it in states in which the subject can live everyday life without impairment. For a treatment to be successful in the long term, it is essential to keep in mind the brain's adaptivity and learning capabilities, and to modulate them in an appropriate way to achieve a healthier brain network which "unlearned" epilepsy.

## 6 Conclusion

Recognizing epilepsy as a network disease has sparked extensive and expanding research, which led to much progress towards the understanding of the human epileptic brain as well as prediction and control of its dynamics. This has reshaped the comprehension and perception of epilepsy, entailing a paradigm shift from a clinically defined epileptic focus via a spatially and functionally extended epileptic network to a large-scale, time-evolving epileptic brain network, whose changes comprise various temporal and spatial scales. Although such an approach poses a difficult task, the last two decades have been coined by novel insights and progression, ranging from recording the brain's structure and dynamics at various spatial and temporal scales to constructing functional brain networks and investigating their properties with various innovative and adapted customized tools of analysis. Insights achieved so far regarding the temporal evolution of the epileptic brain network show great potential for clinical translation, progressing and maturing the state-of-art of diagnosis and treatment of epilepsy. Further studies on the temporal-evolution of epileptic and other diseased brain networks in comparison to non-affected brains will help to achieve these goals.

## Author contributions

TB: Writing–original draft, Writing–review and editing. TR: Writing–original draft, Writing–review and editing. JP: Writing–original draft, Writing–review and editing. RvW: Writing–original draft, Writing–review and editing. KL: Writing–original draft, Writing–review and editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Publisher's note

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