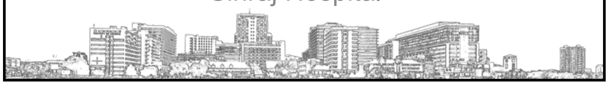
Mahidol University
Faculty of Medicine Siriraj Hospital

Epilepsy as a Network Disorder

Kanokwan Boonyapisit, M.D.
Department of Medicine
Siriraj Hospital



Outline

- Definition
- Zones VS networks
- Early network
- Methods used to study epileptic networks
- Human connectomes projects
- Application of network knowledges in clinical setting

Definition

- Epileptogenic Network
- The brain regions involved in the production and propagation of epileptic activities

Epilepsia, 51(4):676–685, 2010
doi: 10.1111/j.1528-1167.2010.02522.x

SPECIAL REPORT

Revised terminology and concepts for organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005–2009

*†Anne T. Berg, ‡Samuel F. Berkovic, §Martin J. Brodie, ¶Jeffrey Buchhalter, #**J. Helen Cross, ††Walter van Emde Boas, ‡‡Jerome Engel, §§Jacqueline French, ¶¶Tracy A. Glauser, ##Gary W. Mathern, ***Solomon L. Moshé, †Douglas Nordli, †††Perrine Plouin, and ‡Ingrid E. Scheffer

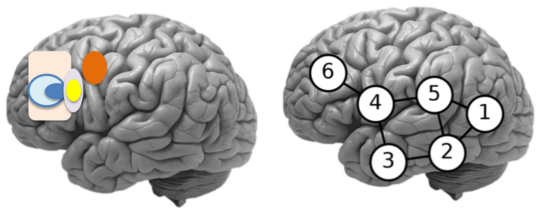
*Department of Biology, Northern Illinois University, DeKalb, Illinois, U.S.A.; †Department of Neurology, Epilepsy Center, Northwestern Children's Memorial Hospital, Chicago, Illinois, U.S.A.; ‡Epilepsy Research Centre, University of Melbourne (Austin Health), West Heidelberg, Victoria, Australia; §Epilepsy Unit, Western Infirmary, Glasgow, Scotland; ¶Department of Neurology, Phoenix Children's Hospital, Phoenix, Arizona, U.S.A.; #Neurosciences Unit, UCL-Institute of Child Health, Great Ormond Street Hospital, London, United Kingdom; **National Centre for Young People with Epilepsy, Lingfield, United Kingdom; ††Department of EEG/EMU, Epilepsy Clinic "Meer & Bosch," Heemstede; Stichting Epilepsie Instellingen Nederland, Hoofddorp, The Netherlands; ‡‡Department of Neurology, UCLA, Los Angeles, California, U.S.A.; §§Department of Neurology, New York University, New York, New York, U.S.A.; ¶¶Department of Neurology, Cincinnati Children's Hospital, Cincinnati, Ohio, U.S.A.; ##Department of Neurosurgery, UCLA, Los Angeles, California, U.S.A.; ***Department of Neurology, Albert Einstein College of Medicine, Bronx, New York, U.S.A.; and†††Department of Neurology, Hôpital Necker Enfant Malades, Paris, France

Epilepsia 2010;51:676-85

Changes in concepts and terminology

- <u>Focal seizure</u>
- originating within networks limited to one hemisphere. They may be discretely localized or more widely distributed. Focal seizures may originate in subcortical structures
- <u>Generalized seizure</u>
- originating at some point within, and rapidly engaging, bilaterally distributed networks

Zones VS Networks



Brain (2001), 124, 1683–1700

INVITED REVIEW

Presurgical evaluation of epilepsy

Felix Rosenow[1] and Hans Lüders[2]

[1]Department of Neurology, Philipps University, Marburg, Germany and [2]Department of Neurology, The Cleveland Clinic Foundation, Cleveland, Ohio, USA

Correspondence to: Hans O. Lüders, MD, Department of Neurology S90, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195, USA
E-mail: scolarc@ccf.org

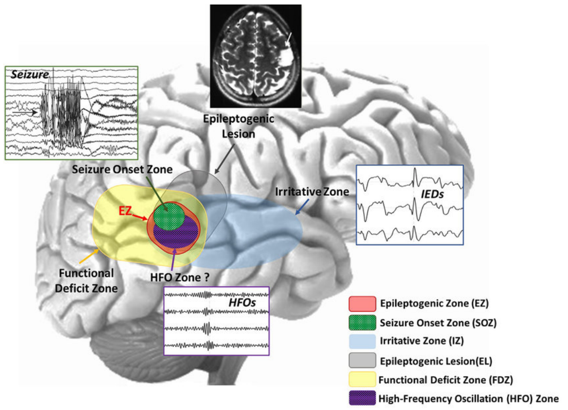
Epilepsia, 43(3):219–227, 2002
Blackwell Publishing, Inc.

Clinical Research

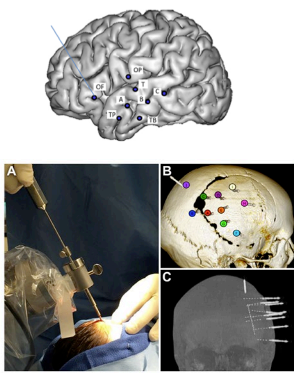
Neural Networks in Human Epilepsy: Evidence of and Implications for Treatment

Susan S. Spencer

Department of Neurology, Yale University School of Medicine, New Haven, Connecticut, U.S.A.



Zones	Definition	What tells what?
Irritative zone	Area that creates interictal epileptiform discharges	Interictal EEG, MEG, EEGfMRI
Ictal onset zone	Origin of EEG seizures	EEG or invasive EEG recording during onset of seizure
Symptomatogenic zone	Area that creates symptoms during seizures	Ictal semiology on video
Epileptogenic lesion	Lesion that create seizures	Neuroimaging
Functional deficit zone	Area that responsible for neurological deficits	Deficit during interictal period
Epileptogenic zone		"Seizure free after resection"



- The concept of epileptogenic networks is historically linked to the development of the stereoelectroencephalography (SEEG) method
- SEEG method was developed in the 1960s by Talairach and Bancaud and consists of stereotactic implantation of multiple intracerebral electrodes targeting different brain areas

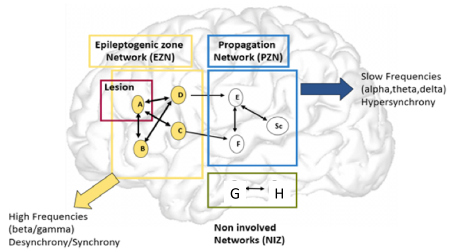
Roland JL, et al. J Neurosurg Pediatr 23:411–421, 2019

- The view arose because the SEEG, for the first time, allowed simultaneous recording from multiple cortical and subcortical structures, which were seen to be concurrently involved in seizure organization, and whose anatomic relation could be precisely defined

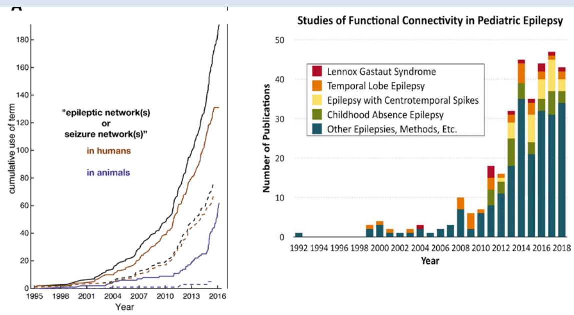
- Early observation from Bancaud and Talairach's SEEG studies
  - The electrical disturbances arising from the presence of an epileptogenic cerebral lesion did not respect anatomic boundaries
  - Seizures could be observed to arise from structures quite distant from the lesion and even separate from the region of maximal interictal spiking

- Original concept of the EZ
- the idea of a set of interrelated brain regions involved in the primary organization of the ictal discharge, rather than a focus

The scheme proposes a hierarchical organization in terms of epileptogenicity in the epileptic brain



Studies of epileptic networks



Bear JJ, et al. Epilepsia. 2019;60:1491–1507.

Methods used to study epileptogenic networks

- Structural (anatomical) studies
  - MRI tractography
  - Covariance of morphologic markers eg. gray matter volume or cortical thickness
- Effective connectivities studies
  - CCEP
- Functional studies
  - fMRI

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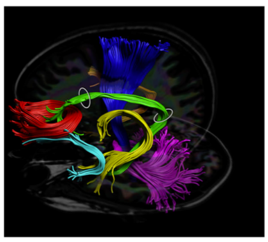
MRI tractography



NMR in Biomedicine. 2019;32:e3785

- Water molecules move better along the fibers than in their perpendicular orientation
- By measuring the dMRI signal for each imaging voxel along a number of noncollinear orientations, the local fiber orientations can be assessed throughout the tissue of interest.
- These local fiber orientations can then be pieced together to construct long-range pathways connecting distant regions of the brain, "fiber tracking or fiber tractography"

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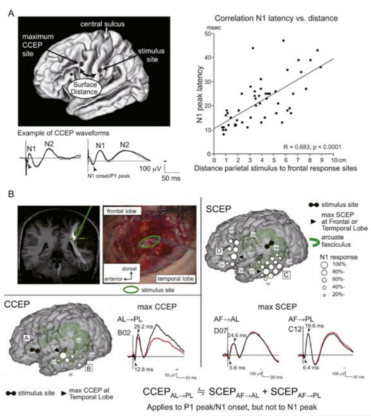
Effective connectivity

- Analyze the causal influence between brain regions
- Non-interventional approaches:
- Observational and therorize causality indirectly by analyzing simultaneous recordings of neural activities to quantify the directionality of functional connections using mathematical measures eg. Granger causality and dynamic causal modeling

Effective connectivity

- Interventional approaches:
- Use stimulation (cortical stimulation transcranial magnetic stimulation)
- to influence changes recorded by evoked responses recorded on EEG or electrocorticogram (ECoG)) or recorded indirectly by fMRI in order to assess its effects on other brain regions



Matsumoto R, et al. Seizure 2017; 44:27–36.

CCEP connectivity studies to probe functional brain networks.

Direct cortical responses	
Functional cortical characterization	Goldring et al. [8]
Language system	
Dorsal language network	Matsumoto et al. [12], Conner et al. [33], Keller et al. [23], Enatsu et al. [65] David et al. [15], Yamao et al. [25][a], Saito et al. [26][a], Tamura et al. [27][a]
Ventral language network	Matsumoto et al. [12], Umeoka et al. [1], Koubeissi et al. [2], Araki et al. [22]
Cognitive motor system	
preSMA/SMA-lateral PM/MI	Matsumoto et al. [19], Kikuchi et al. [49][a], Swann et al. [3]
Negative motor network	Enatsu et al. [71]
Interhemispheric connections	Terada et al. [20,21]
Fontal lobe network	
IFG connectivity	Greenlee et al. [67,68], Garell et al. [34]
Fronto-parietal connectivity	Matsumoto et al. [29]
Fronto-temporal connectivity	Lacruz et al. [60]
Limbic network	
Limbic pathways	Wilson et al. [9], Catenoix et al. [66], Kubota et al. [19], Koubeissi et al. [43], Lacuey et al. [42], Enatsu et al. [5]
Interhemispheric connections	Wilson et al. [10], Umeoka et al. [1], Jimenez-Jimenez et al. [6]
Insular connectivity	Almashaikhi et al. [8]
Auditory system	
A1-pSTG connectivity	Howard et al. [13], Brugge et al. [64], Oya et al. [70]
Visual system	
V1-higher visual cortices	Matsuzaki et al. [69]
Thalamo-cortical network	
Pulvinar-cortices	Rosenberg et al. [16]
Connectivity maps	
BA parcellation map	Entz et al. [44]
Comparison with ECoG broadgamma envelope	Keller et al. [24,61]
Comparison with resting state fMRI	Keller et al. [23]
Comparison with diffusion tractography	Donos et al. [45]

SMA = supplementary motor area; PM = premotor area; MI = primary motor area; IFG = inferior frontal gyrus; A1 = primary auditory cortex; V1 = primary visual cortex; BA = Brodmann's area.

[a] Intraoperative studies.

Matsumoto R, et al. Seizure 2017; 44:27–36.

Methods used to study epileptogenic networks

- Structural (anatomical) studies
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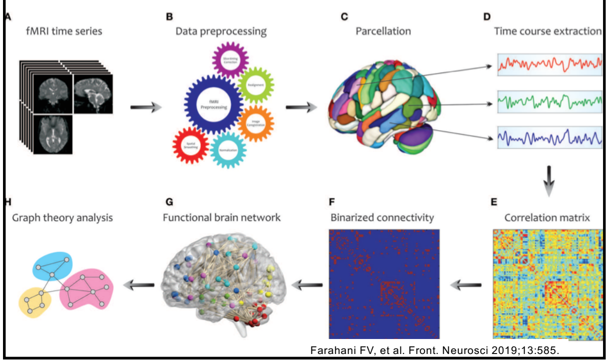
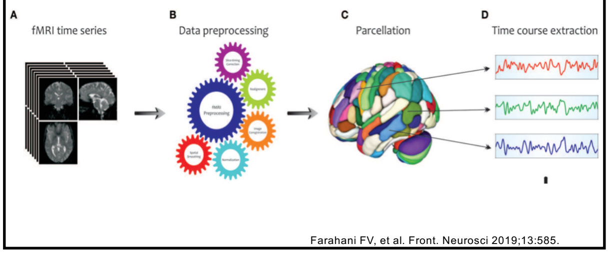
fMRI studies of connectivity



Farahani FV, et al. Front. Neurosci 2019;13:585.

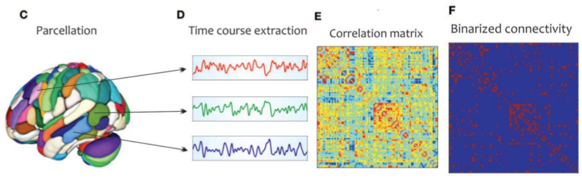
How to define nodes?

- Various criteria can be used to define nodes
- eg. single voxels, anatomic parcellations



Farahani FV, et al. Front. Neurosci 2019;13:585.

- By globally mapping pairwise connections between given numbers of nodes, a connectivity matrix can be constructed



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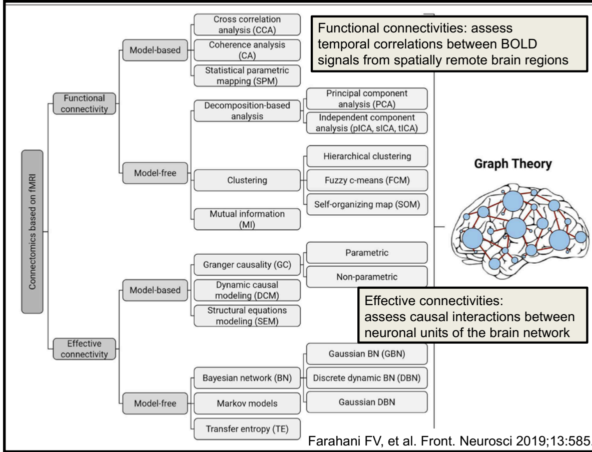
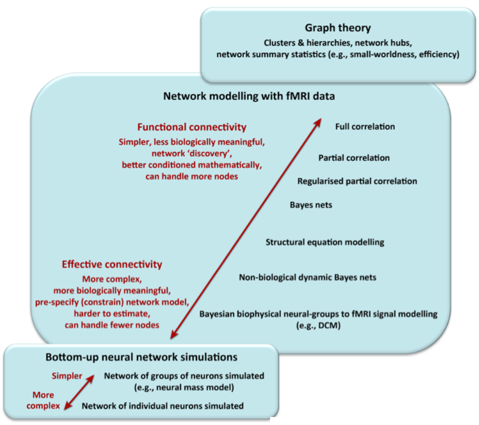


Functional connectivities: assess temporal correlations between BOLD signals from spatially remote brain regions

Effective connectivities: assess causal interactions between neuronal units of the brain network

Farahani FV, et al. Front. Neurosci 2019;13:585.



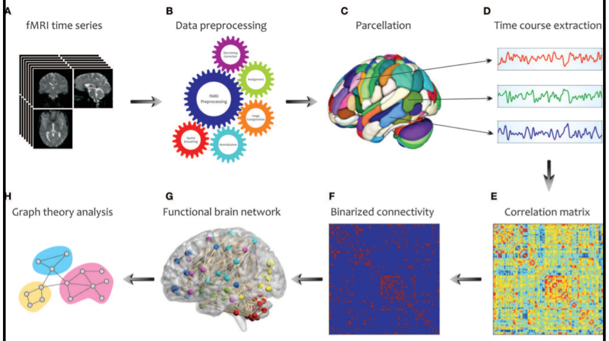
Trends in Cognitive Sciences 2013; 17:666

Common terminology and methods used in functional connectivity studies

Method/concept	Description	Advantages/considerations
FC	Relationships between spatially separated brain regions inferred from statistically correlated brain activity. In this paper, we use "functional connectivity" to imply undirected measures and "efferent connectivity" (see below) for directed measures, a common convention. Although far from exhaustive, some of the more common measures of FC include Pearson correlation coefficient, coherence, phase lag index, and phase-locking value.	Allows noninvasive in vivo measurement of the brain state at a macroscopic level. The measured state is a result of combined excitatory and inhibitory activity at any given time window and in general is not capable of differentiating excitatory from inhibitory activity. Unlike efferent connectivity, calculating FC is often computationally straightforward and may have greater test-retest reliability but lacks inferences on directionality.
Directed (effective) connectivity	Statistical inferences about the relationship between spatially separated brain regions using methods that identify the direction of information flow. Some of the common approaches include Granger causality, DCM, phase slope index, and partial directed coherence.	Informative approach to studying networks that provides an understanding of how information is processed or, in epilepsy, how seizures and other pathologic phenomena propagate. Can be computationally complicated and intensive, and some methods like DCM require strong a priori hypotheses for interpretation.
Dynamic functional connectivity	Assessment of functional and effective connectivity changes over time, often over a period of seconds or minutes.	Gives insights into the temporal evolution of brain networks. As FC measurements cannot be made instantaneously (time series data are required), decisions about time windows and computational methods will affect results.
ALFF	Averaged square root of fMRI-based activity in the low-frequency band (0.01-0.08 Hz). Although not a true measure of functional connectivity per se, ALFF maps can inform FC measurements and have shown spatial distributions similar to FC-derived networks.	In the context of childhood epilepsy, ALFF is most often used to identify ROIs for subsequent connectivity measurements.
ReHo	fMRI-based measure of the relationship between close brain regions, usually defined as within 10-15 mm. In practice, ReHo calculates Kendall coefficient of concordance between every given brain voxel and its nearest neighbors to generate a whole brain ReHo map.	Novel centrality metric of brain regions within the whole connectome. Potential method for parcellating individual brains, as decreases in ReHo are expected at the borders between functional cortical parcels. Interpretation of ReHo differences is complicated by a smaller body of research compared to more traditional FC measurements.
ICA	Signal processing method of separating a multivariate signal into its subcomponents. Often used to derive the spatial components of the brain's intrinsic networks.	Well-established method for deriving distinct brain networks. Selection of computational variables can be arbitrary and yield differential results. Robust and reliable in large datasets but of limited utility in individual subjects.
Graph theory and related measures	The most common mathematical framework used to study networks, which are represented mathematically as graphs. Graph theory–based measures are available to describe and analyze extensive features of brain networks.	Critical methods for network analysis. Application of graph theory is complicated by dozens of potential network measurements, many of which provide only subtle distinctions and many of which collapse the spatial network information.

Abbreviations: ALFF, amplitude of low-frequency fluctuations; DCM, dynamic causal modeling; f
connectivity; ICA, independent component analysis; ROI, region of interest; ReHo, regional homo

Bear JJ, et al. Epilepsia. 2019;60:1491–1507.

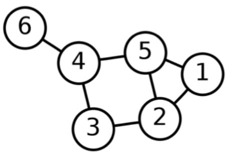


Farahani FV, et al. Front. Neurosci 2019;13:585.

Graph Theory

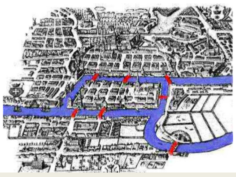
- the study of graphs, which are mathematical structures used to model pairwise relations between objects
- a framework for the mathematical representation and analysis of complex systems
- Provides a powerful formalism to quantitatively describe the organizational patterns of brain networks.
- Its application to neuroimaging data has revealed novel insights into normal brain function and epilepsy

- **graph** is a diagram of a set of objects in which some pairs of the objects are in some sense "related"



6 Nodes (vertices)

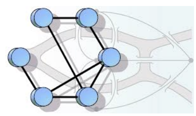
7 Edges

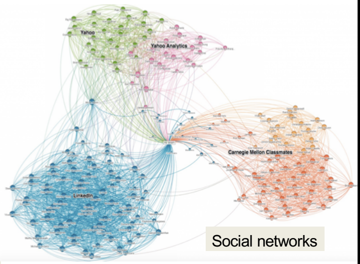


The paper written by Leonhard Euler on the Seven Bridges of Königsberg and published in 1736 is regarded as the first paper in the history of graph theory.

The challenge with Königsberg's bridges, was to be able to walk through the city by crossing all the seven bridges only once

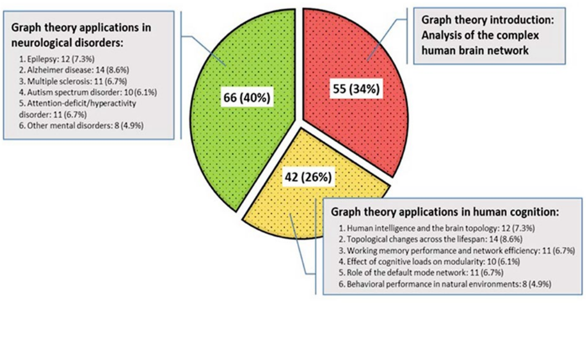
- You cannot uncross any bridge
- Each bridge must not be crossed more than once





Social networks

Find shortest distance on maps



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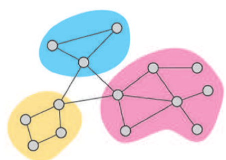
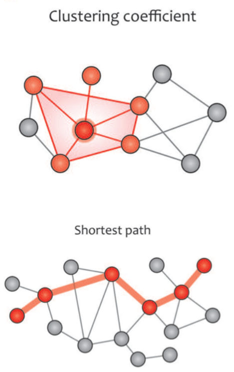
Graph Theory

- Network is composed of
- Nodes (vertex): brain region
- Edges: structural or functional connections



- Clustering coefficient (C): likelihood that neighbours of a vertex will also be connected, is a measure for the tendency of network elements to form local clusters
- Characteristic path length (L): the average of the shortest distance between every pairs of vertices counted as a number of edges. The characteristic path length L indicates how well network elements are integrated or interconnected



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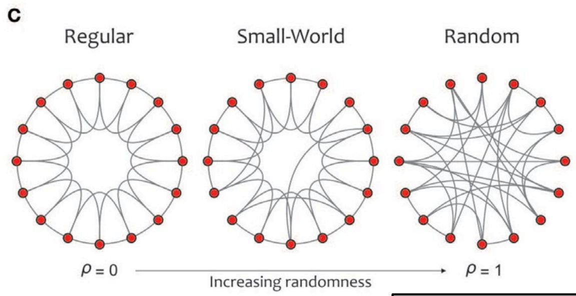

High clustering coefficient Long average path length	High clustering coefficient Short average path length	Low clustering coefficient Short average path length

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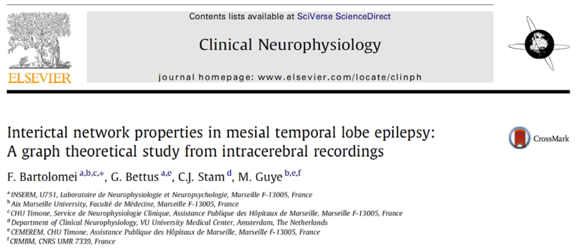

Contents lists available at SciVerse ScienceDirect

Clinical Neurophysiology

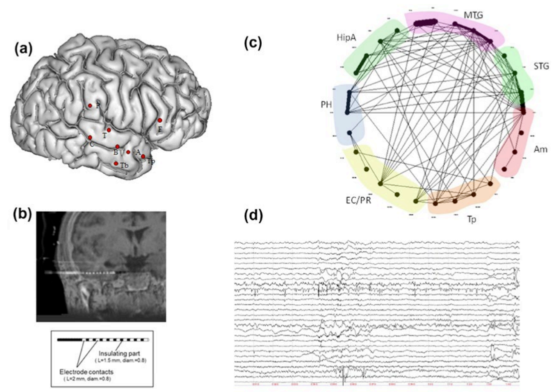
journal homepage: www.elsevier.com/locate/clinph

Interictal network properties in mesial temporal lobe epilepsy: A graph theoretical study from intracerebral recordings

F. Bartolomei [a,b,c,*], G. Bettus [a,e], C.J. Stam [d], M. Guye [b,e,f]

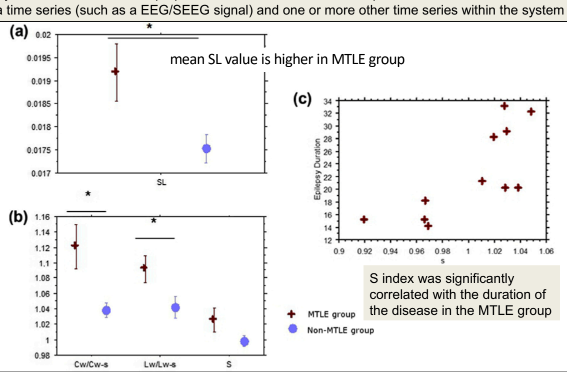
- Study investigating complex network properties based on interictal intracerebral EEG in temporal lobe epilepsy (TLE).
- Compared a group of patients with mesial TLE with a "control group" having neocortical epilepsy(non MTLE) by calculating synchronization between 28 signals from mesial temporal lobe and some neocortical regions.
- Results are in favor of a more regular (less random) configuration of epileptogenic networks (increased normalized clustering index).

Clinical Neurophysiology 2013;124:2345–53



Clinical Neurophysiology 2013;124:2345–53

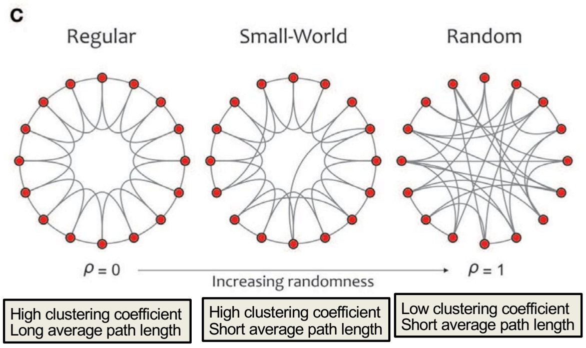
Synchronization likelihood (SL): a measure for statistical interdependencies between a time series (such as a EEG/SEEG signal) and one or more other time series within the system



S index was significantly correlated with the duration of the disease in the MTLE group

Clustering coefficient (Cw) is higher in MTLE group
Path length (Lw) is slightly higher in MTLE group
Small world index (S) is higher in MTLE group

- The parallel increase of both C and L parameters is indicating of a more regular configuration
- These results are in agreement with previous studies in human epilepsy using different functional approaches such as MEG (Chavez et al., 2010; Horstmann et al., 2010) but discordant results were found in studies using resting-state fMRI studies that found different topology alteration of functional networks (Liao et al.,2010; Vlooswijk et al., 2011).



Farahani FV, et al. Front. Neurosci 2019;13:585.

- The identification of such more regularized topology could be considered as a new biomarker of epileptogenic network potentially useful for the presurgical evaluation.
- Nevertheless, correlations between clinical parameters and graphs parameters are still to be performed on larger cohorts of patients.
- This result is also in agreement with a previous study suggesting that neural networks in TLE patients become more pathological over time (van Dellen et al., 2009).

Evidence of disrupted network topology in TLE: insights from graph theory

- The application of graph theory, along with clinico-radiological findings, helps to better understand the network mechanisms behind a cognitive decline in focal epilepsies, particularly TLE, and offers promising diagnostic biomarkers

Chiang and Haneef 2014; Onias et al. 2014; Wang et al.2014; Pedersen et al 2015; Ridley et al. 2015; Iyer et al. 2018

Evidence of disrupted network topology in TLE: insights from graph theory

- A study of brain networks from resting state fMRI reported decreased clustering and path length, and disruptions in the distribution of network hubs, in favor of a random network topology (Liao et al., 2010).
- However, a more recent study showed increased clustering and path length, a finding rather typical of a regular topology (Wang et al., 2014), which are in line with graph-theory analysis of structural networks constructed from
  - Cortical thickness correlations (Bernhardt et al., 2011)
  - Diffusion MRI data (Bonilha et al., 2012; Liu et al., 2014)
  - Electrophysiology-derived network analyses (Bartolomei et al., 2013).

Caciagli L, et al. Front Neurosci 2014;8

Evidence of disrupted network topology in TLE: insights from graph theory

- Evidence from some of the studies suggests that alterations in brain structural (Bernhardt et al., 2011) and functional (Wang et al., 2014) networks intensify over time.
- Certain studies have shown that patients with a poor outcome after surgery exhibit more pronounced network disruptions compared to those who achieved seizure freedom.
- These findings suggest that whole-brain network analysis might be a valuable asset for clinical decision-making (Bernhardt et al., 2011).

Caciagli L, et al. Front Neurosci 2014;8

Epilepsy network is dynamic

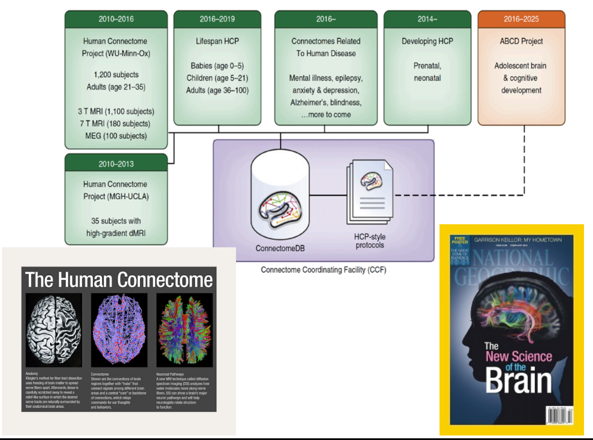
- Wide spread zone
- May have
  - inter-seizure variation
  - multiple networks
  - inter-individual variation
- May progress overtime

Studies on epileptic networks: Caveats

- Although the contribution of aberrant connectivity to seizure control is increasingly recognized, individualized predictive values on a single-patient level remain to be established, because most studies so far have focused on group analyses
- Understanding the complexities between the epileptogenic zone/lesion and whole-brain connectivity is of special importance for clinical decision making in epilepsy surgery and should be the object of future in-depth, possibly prospective, analyses.

Human Connectome Projects

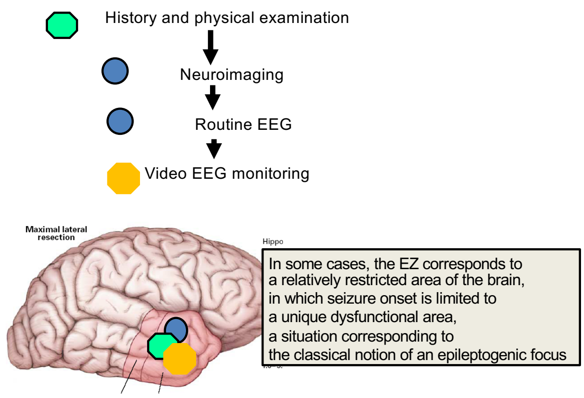
- Began in 2010
- National Institutes of Health (NIH) awarded ~$40 million to two consortia to develop improved neuroimaging methods and to acquire a data set of unprecedented size and quality for mapping the "normal human macroscale connectome" (the long-distance connections between all of the brain's areas)
- Deepen our understanding of healthy brain function and may improve our ability to understand and treat neurological and psychiatric disorders



Application of network knowledges in clinical setting

- Potentially informed seizure focus localization (in complement with other methods)
- Potential predictors of seizure outcome
- Potential predictors of cognitive outcome

Foit NA, Bernasconi A, Bernasconi N. Neurosurg Clin N Am 2020;31:395–405



- However, in many cases the seizure onset is characterized by discharges that simultaneously or very rapidly involve several distributed brain regions. In this situation, the model of the epileptogenic focus cannot accurately describe the spatial organization of the EZ.

Summary

- Definition
- Zones VS networks
- Early network
- Methods used to study epileptic networks
- Human connectomes projects
- Application of network knowledges in clinical setting

Summary

- Since the early works of Bancaud and Talairach using SEEG, multiple approaches have been developed to study the spatiotemporal oscillatory dynamics of brain networks engaged in epileptogenic processes

Summary

- Efforts to quantify the complex phenomena that rule the spatiotemporal organization of the EZ are feasible, but how these concepts may be useful in clinical practice remains uncertain and underapplied
- Potential uses of these concepts could be to
  - improve surgery procedures via tailored and minimally invasive curative surgery based on specific disconnection or multiple nodal targeting
  - informed seizure focus localization (in complement with other methods)
  - predictors of seizure outcome
  - predictors of cognitive outcome