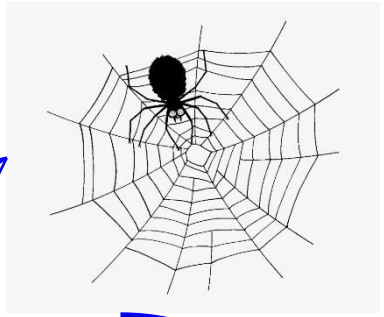
Epilepsy Network in Real-life Practice

Assoc. Prof. Chaiyos Khongkhatithum, MD
Division of Neurology
Department of Pediatrics
Faculty of Medicine Ramathibodi Hospital

Epilepsy network in real-life practice



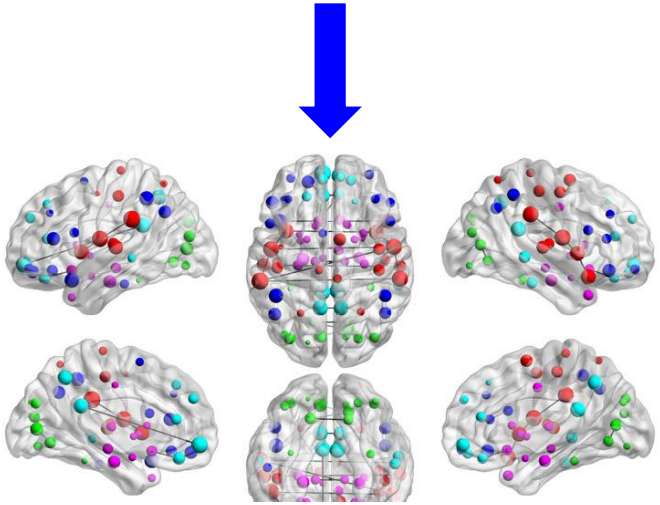
Seizure?→Epilepsy syndrome?→Etiology?→Treatment?

Understanding the Complexity of Epilepsy

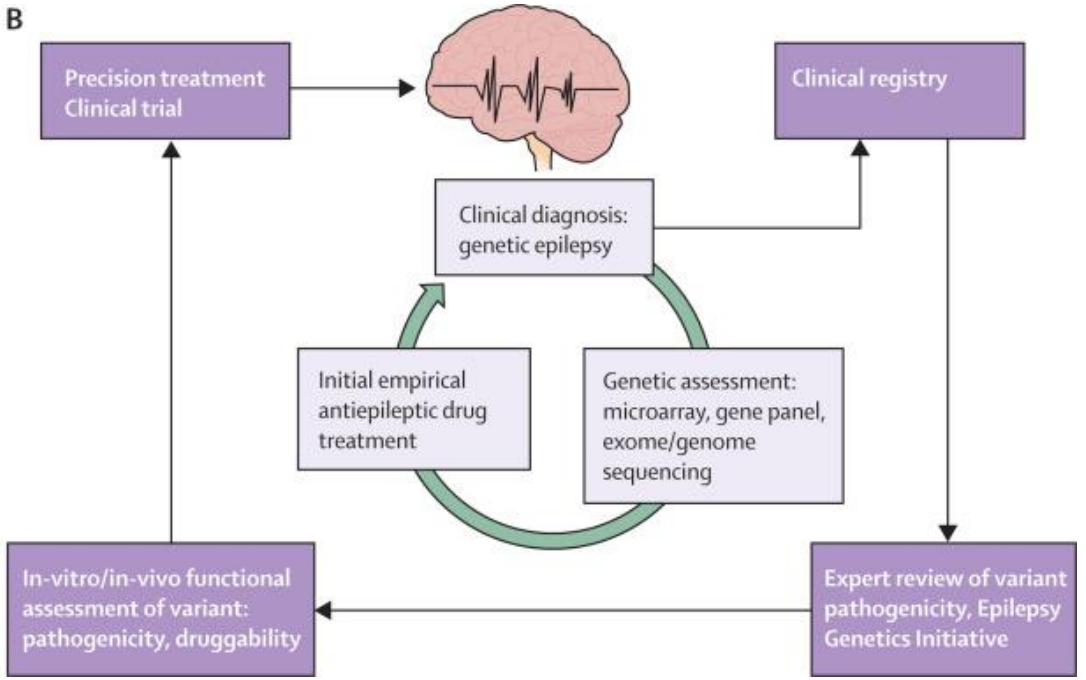
- Understanding disease mechanisms
- Difficult to treat
- Failure of epilepsy surgery
- Innovative treatment e.g. DBS, RNS

Precision Medicine

Seizures/Epilepsy



Medicine??? Surgery +++



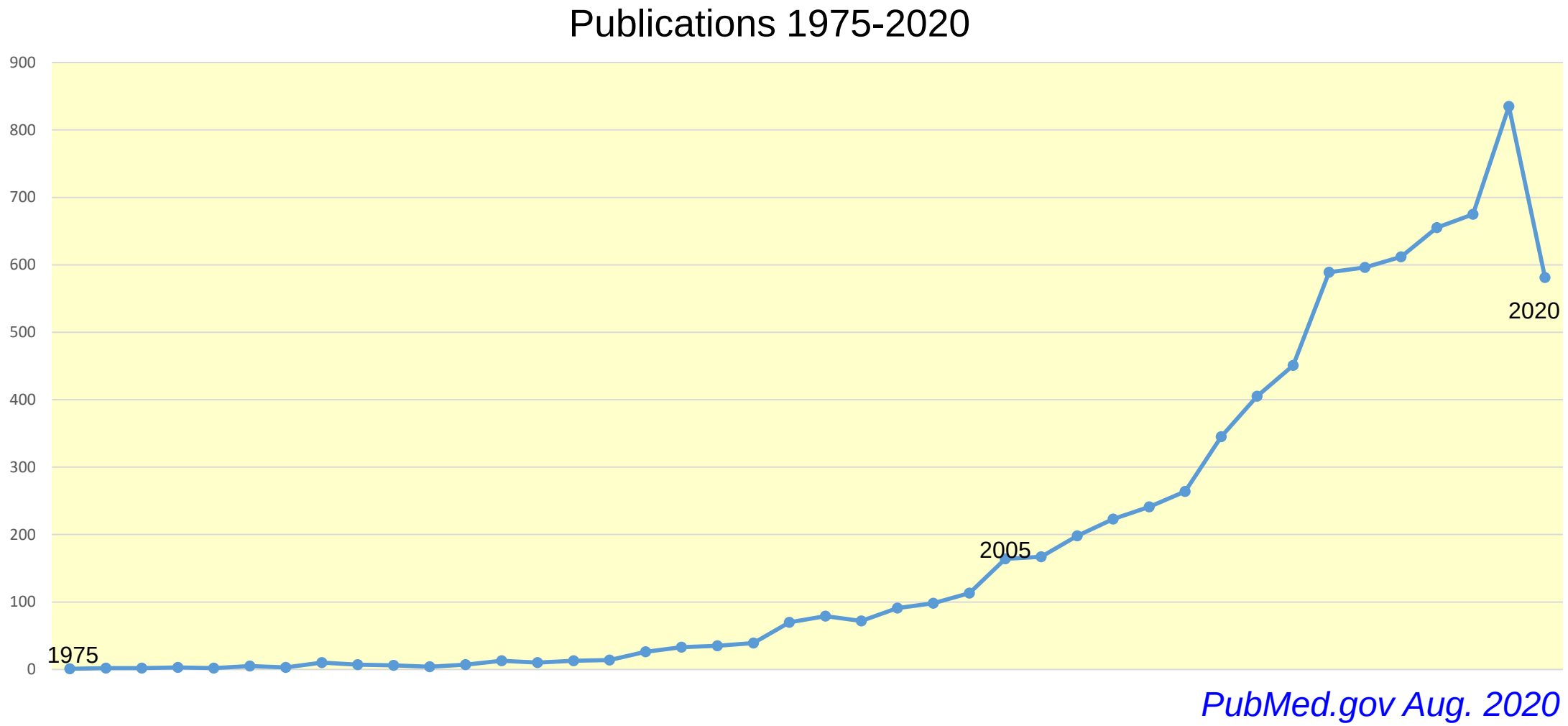
EpiPM Consortium.Lancet Neurol 2015; 14: 1219-28

Gene mutations
- *SCN1A*
- *SCN2A, SCN8A*
- *KCNT1*
- *SLC2A*

Treatments
- CBD, Fenfluramine
- Na-blocker
- Quinidine
- Ketogenic diet

New way of understanding, diagnosing, and potentially treating the various forms of epilepsy

Epilepsy Network



Epilepsy Network: Definition

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

Susan S. Spencer

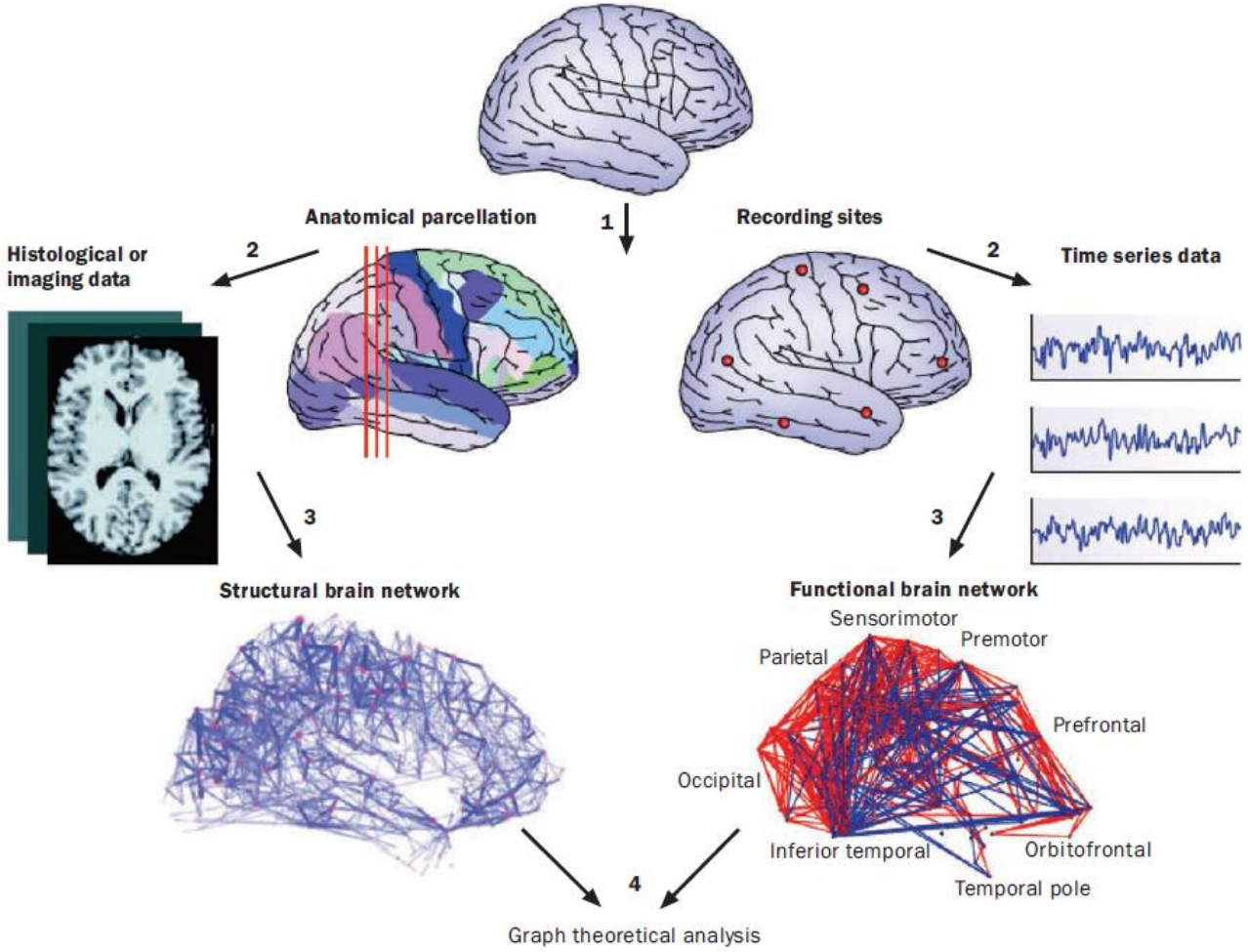
Department of Neurology, Yale University School of Medicine, New Haven, Connecticut, U.S.A.

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 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 S. Epilepsia. 2002;43:219-27.

Epilepsy Network:Concept



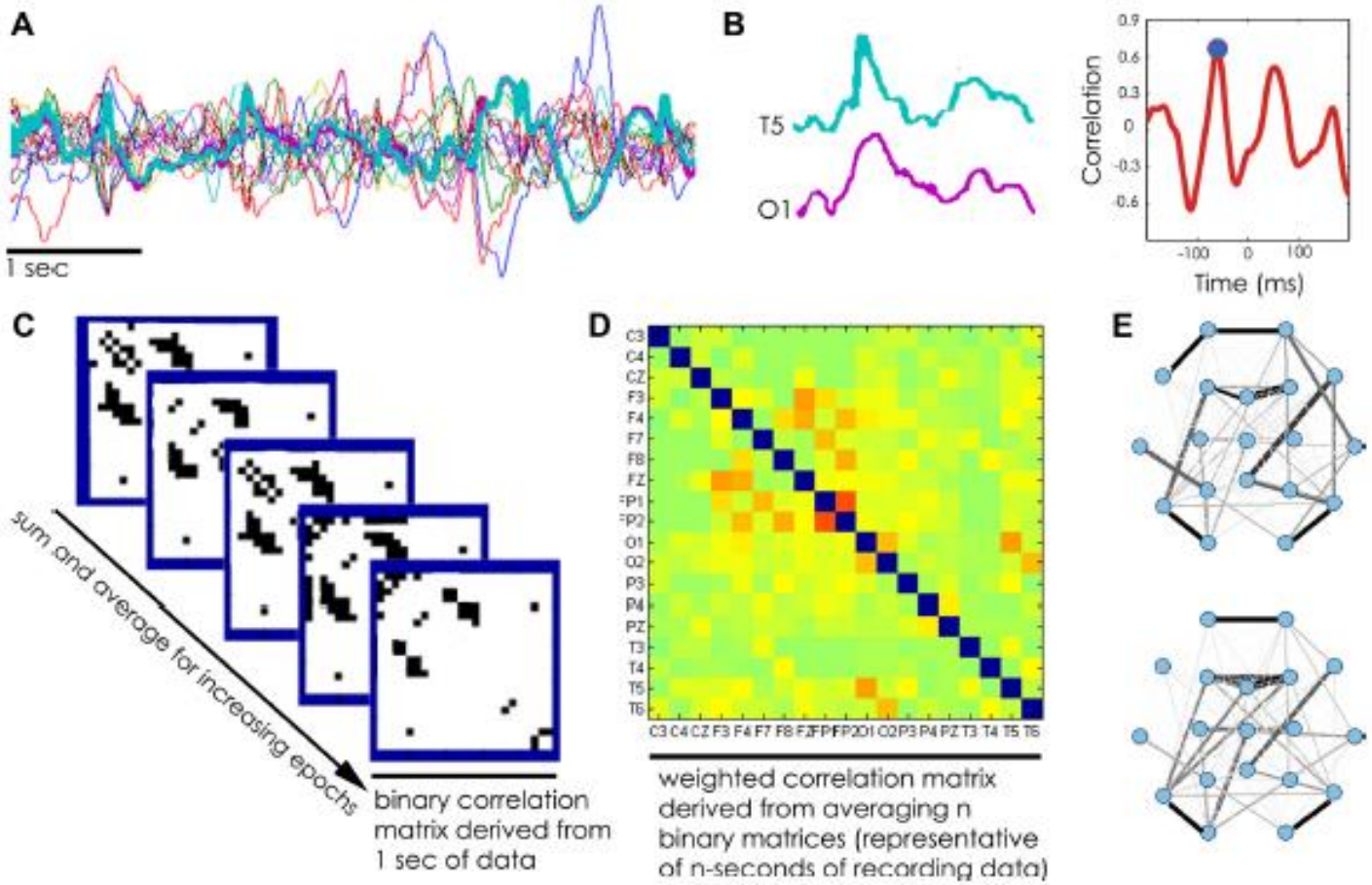
Bassett D. Network Approaches to Diseases of the Brain. 2012;Chapter 4:32-50.

Epilepsy Network

- Complex network analysis
  - Mathematical study of networks (graph theory)
  - Characterize these brain networks with a small number of neurobiologically meaningful and easily computable measures.
- Measures
  - EEG functional connectivity (Quantitative measures)
  - Function MRI (fMRI)
  - Diffusion Tensor Imaging (DTI)
  - MEG
- Comparisons of structural or functional network topologies between subject populations reveal presumed connectivity abnormalities in neurological and psychiatric disorders

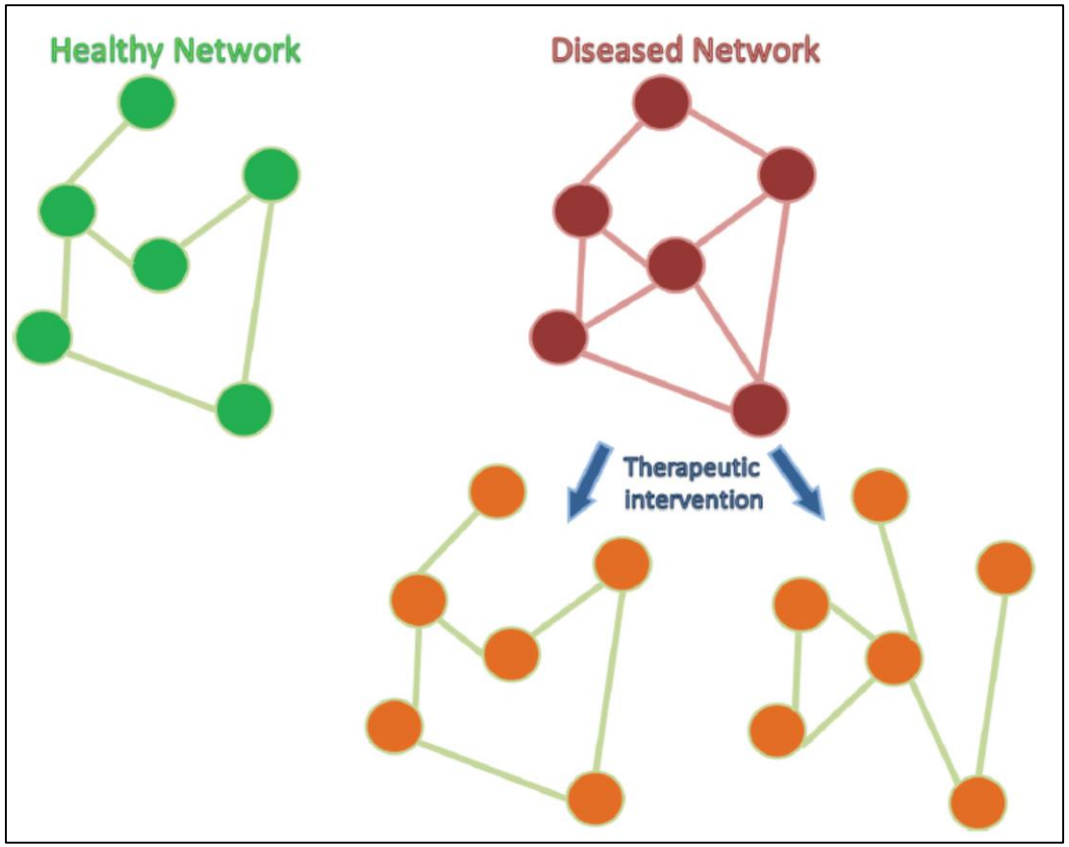
Rubinov M. Neuroimage. 2010;52:1059-69.

Emergence of Stable Functional Networks in Long-Term Human Electroencephalography



Chu C, et al. J Neurosci. 2012;32(8):2703-13.

Epilepsy Network: Healthy and Diseased Networks



Normal Modified

Over-connected or hypersynchrony in an epileptic brain

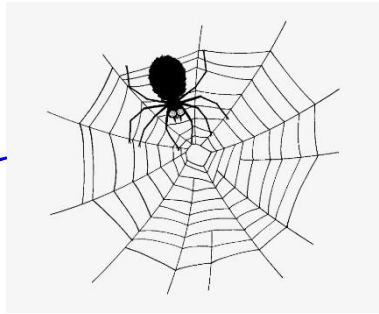
Scott RC. F1000Res. 2016;5:F1000 Faculty Rev-893.

Epilepsy Network: Human

- Three specific large human epilepsy networks
  - **Medial temporal/limbic network**
  - **Medial occipital/lateral temporal network**
  - **Superior parietal/medial frontal network**
  - Bifrontal/pontine/subthalamic network
  - Parietal/medial temporal network

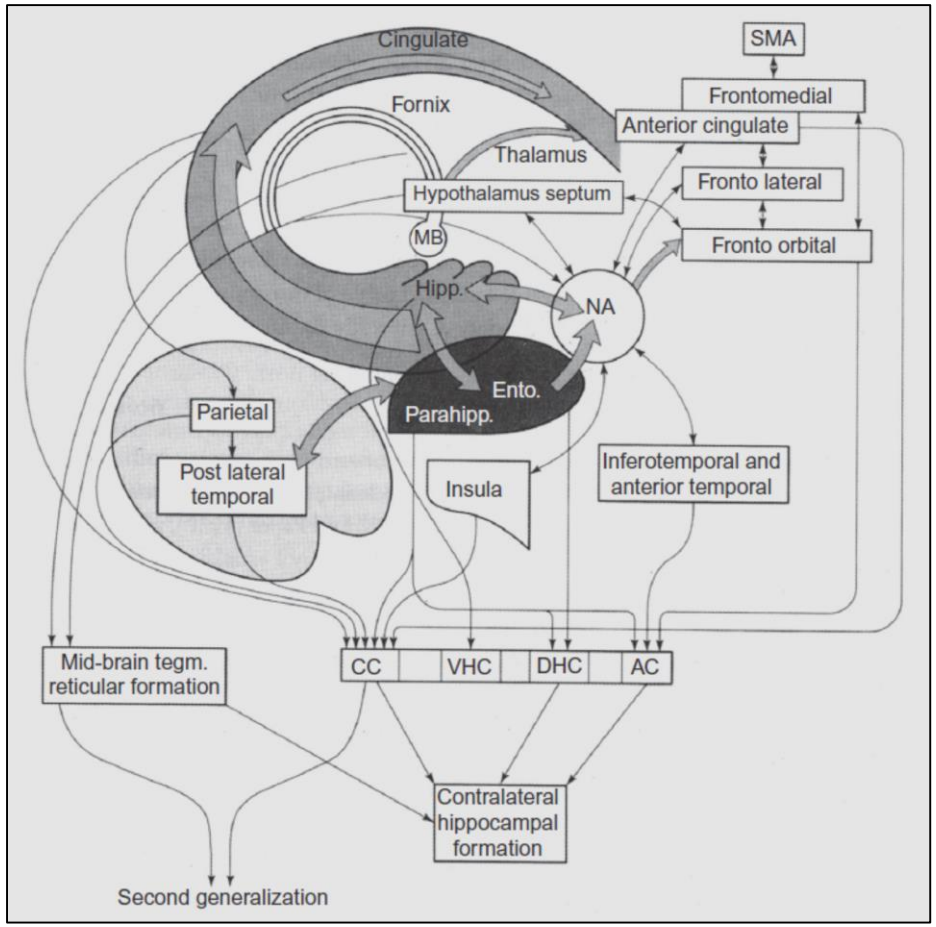
Spencer S. Epilepsia. 2002;43:219-27.

Epilepsy network in real-life practice



Seizure?→Epilepsy syndrome?→Etiology?→Treatment?

Epilepsy Network: Seizure/Semiology



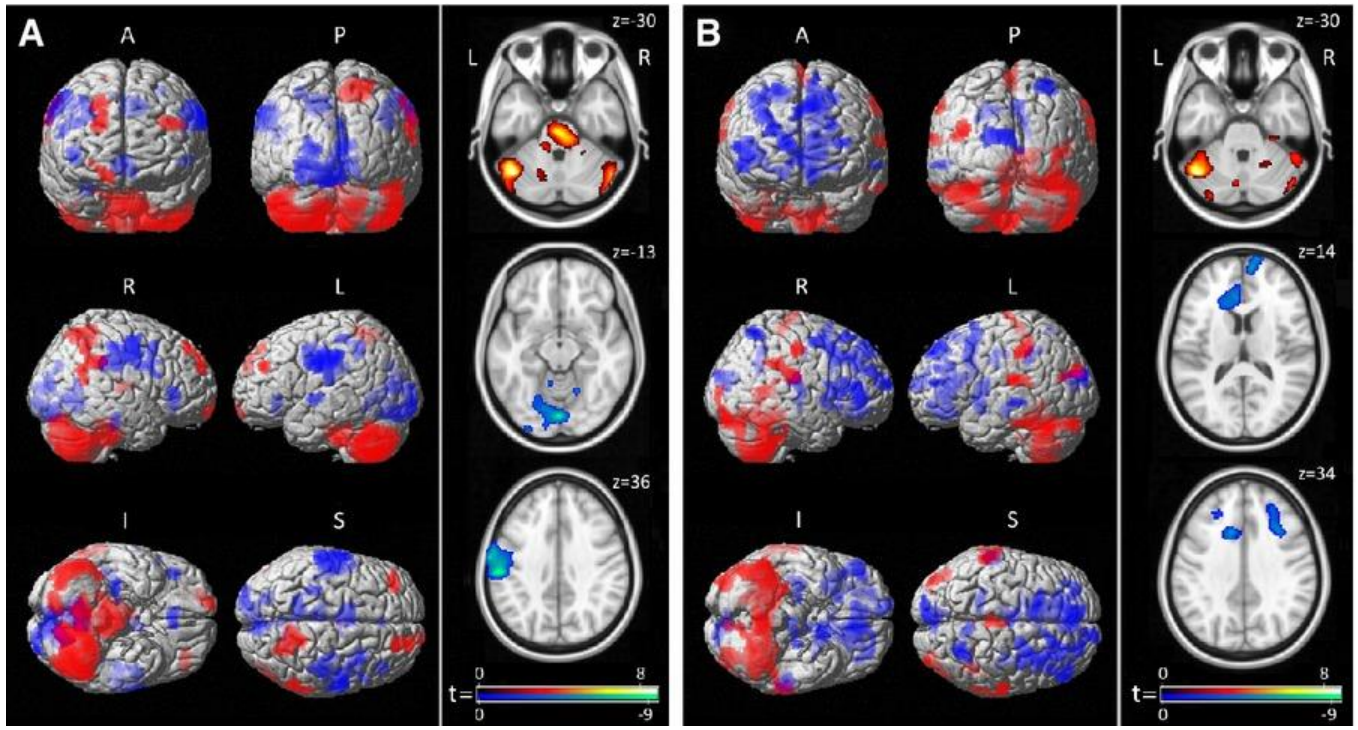
Medial temporal/limbic network

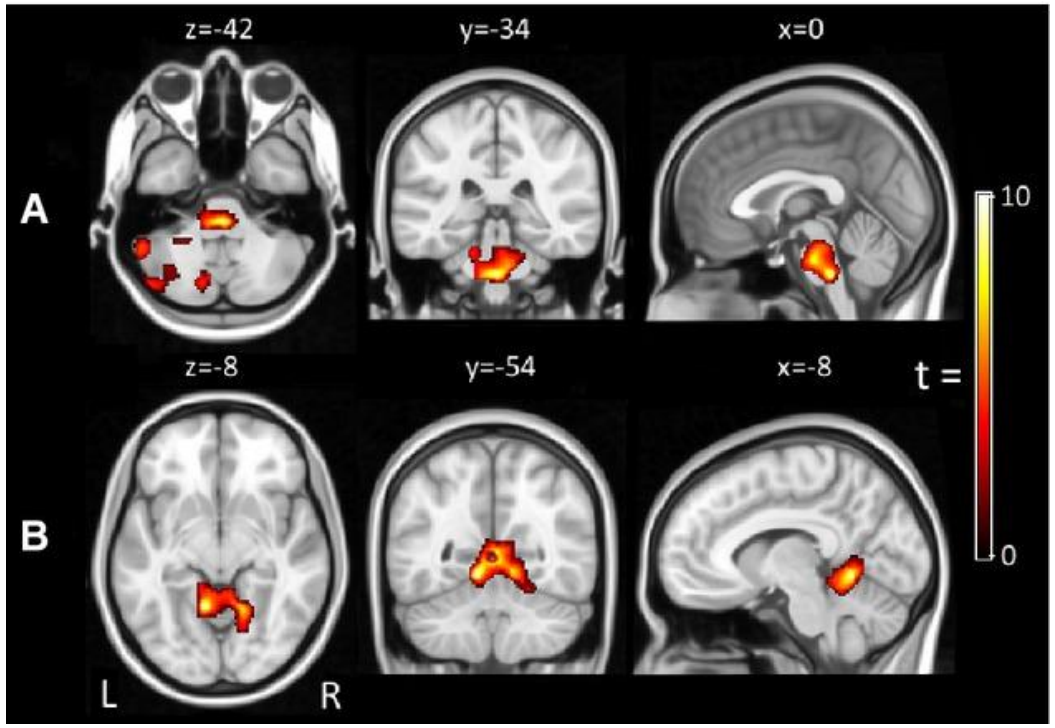
Clinical feature	Involved brain regions
Olfactory hallucinations	Anterior mesial temporal or orbitofrontal
Gustatory hallucinations	Insula/peri-insular, parietal operculum
Fear	Amygdala
Auditory hallucinations	Lateral temporal neocortex
Vestibular symptoms	Lateral temporal neocortex
Visual hallucinations	Occipital lobe
Decreased level of consciousness	Default mode network, bilateral mesial temporal
Oroalimentary automatisms	Amygdala
Head deviation	Frontal lobe

Epigastric rising+Fear→Automatisms+LOC→Head deviation

Reid AY. Int Rev Neurobiol. 2014;114:89-120.

Epilepsy Network: Seizure/Semiology





A. Early injection group (n = 3), ictal hyperperfusion over bilateral fronto-parietal cortices with hypoperfusion over bilateral pericentral and mesial occipital regions
B. Late injection group (n = 7), hyperperfusion over bilateral parietal cortices and diffuse cerebellum, reduced perfusion over both frontal lobes

Tonic seizures of LGS ←→ "Corticopontine network"

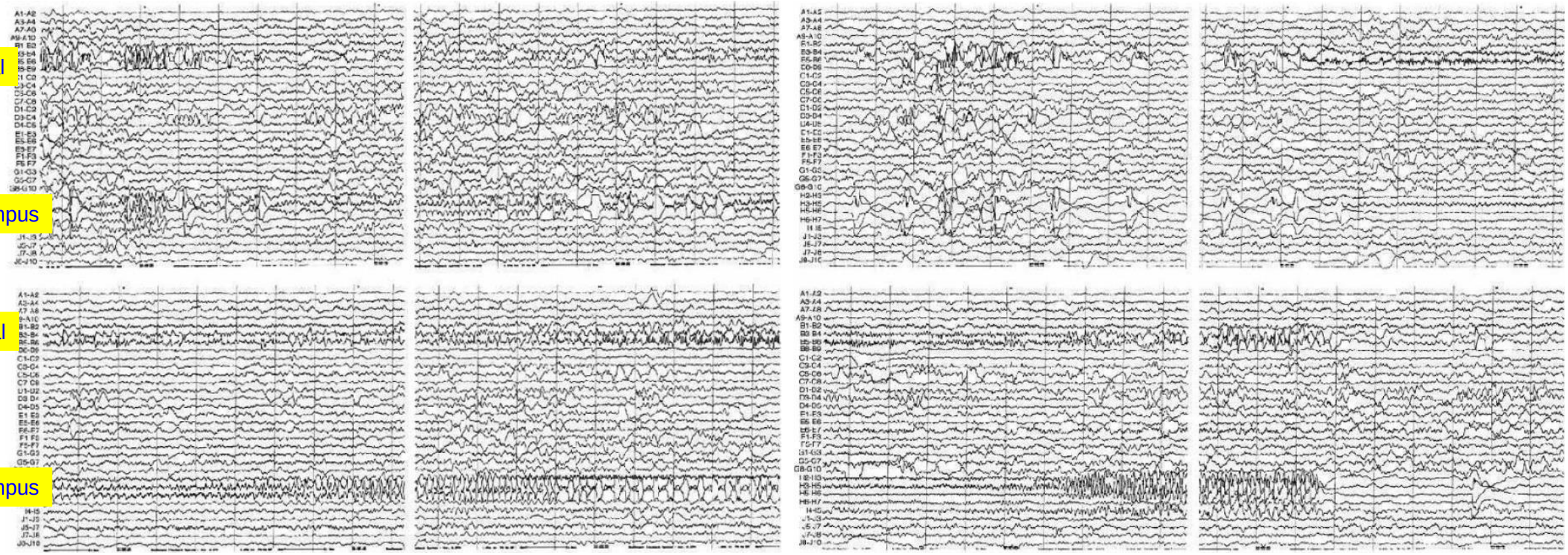
Intusoma U. Epilepsia. 2013;54:2151-57.

Epilepsy Network: Invasive EEG

- Despite variability in the early electrical patterns, clinical seizures are stereotyped, a key observation that truly reflects the operation of the epilepsy network.
- The initial area of apparent seizure involvement is not really an onset area, because “onset” could be expressed any place in the network, and might even vary from seizure to seizure in a given patient.
- Variability in clinical seizures is likely to reflect propagation of seizure activity.

Spencer S. Epilepsia. 2002;43:219-27.

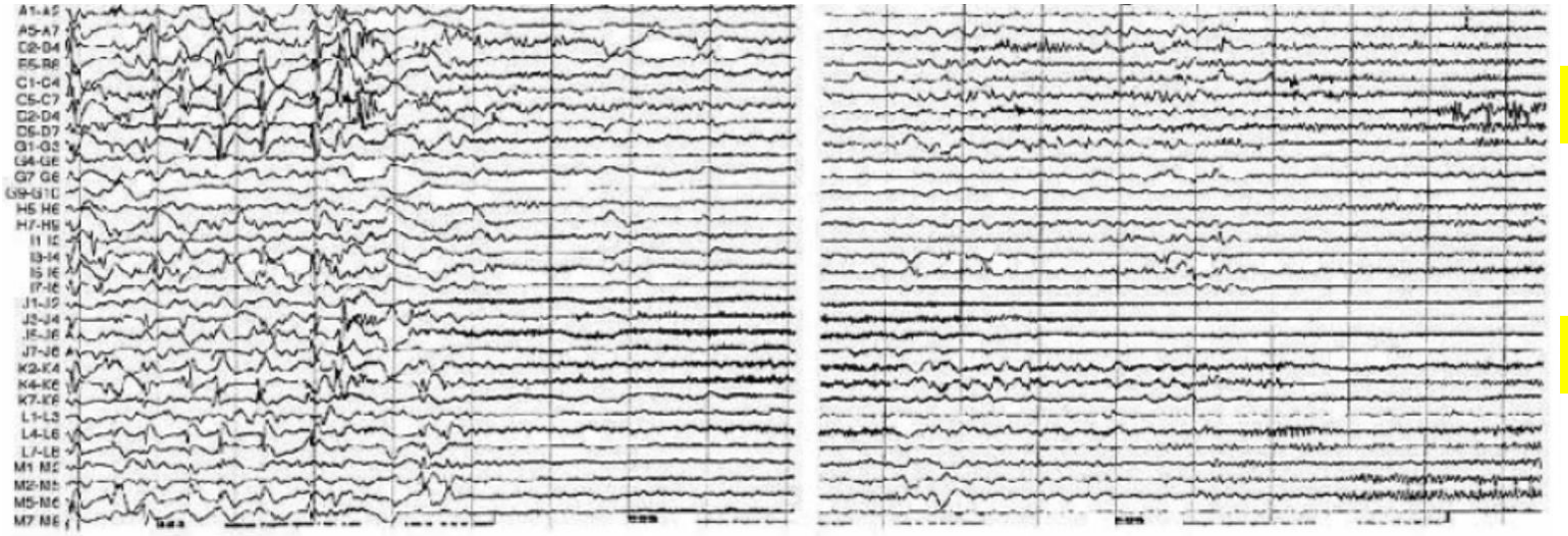
Two spontaneous seizures with identical clinical expression in a patient with the medial temporal limbic network



Spencer S. Epilepsia. 2002;43:219-27.

Two spontaneous, typical, and clinically identical seizures in a patient with epilepsy in the occipitotemporal network.

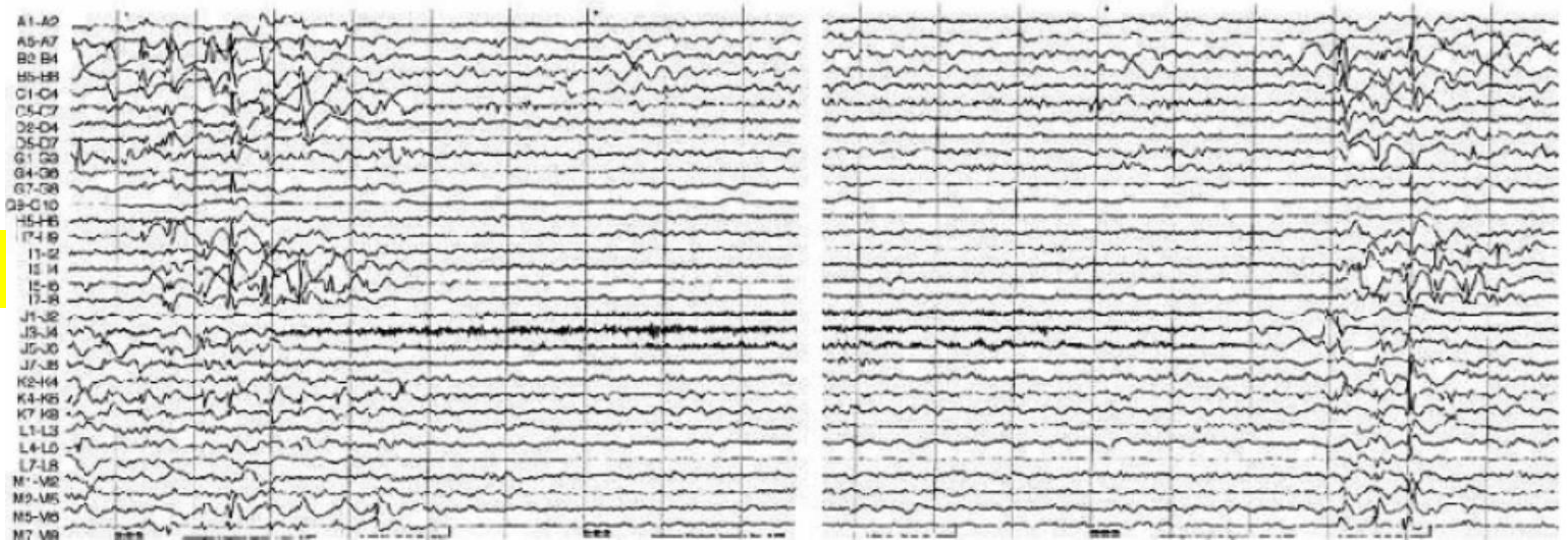
Sz. #1



Temporal*

Occipital*

Sz. #2



Temporal

Occipital*

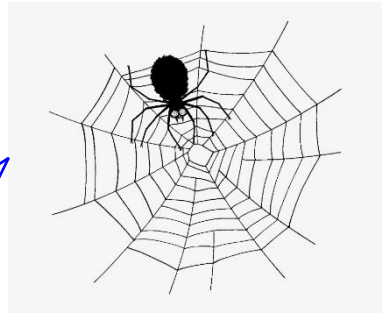
Spencer S. Epilepsia. 2002;43:219-27.

Epilepsy Network: Comorbidity

- Systematic review critically assesses structural and functional neuroimaging studies from 18 studies of adults with psychosis of epilepsy (POE).
  - ➢Conflicting evidence of volumetric change in the hippocampus and amygdala
  - ➢Distributed structural pathology beyond the mesial temporal lobe
  - ➢Changes in frontotemporal functional network activation
- Strong evidence for POE as a disease of brain networks

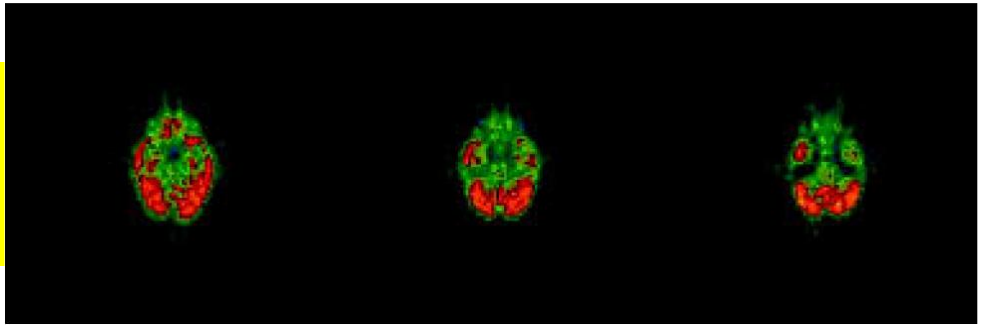
Allebone J. J Neurol Neurosurg Psychiatry. 2018;89(6):611-17.

Epilepsy network in real-life practice



Seizure?→Epilepsy syndrome?→**Etiology?→Treatment?**

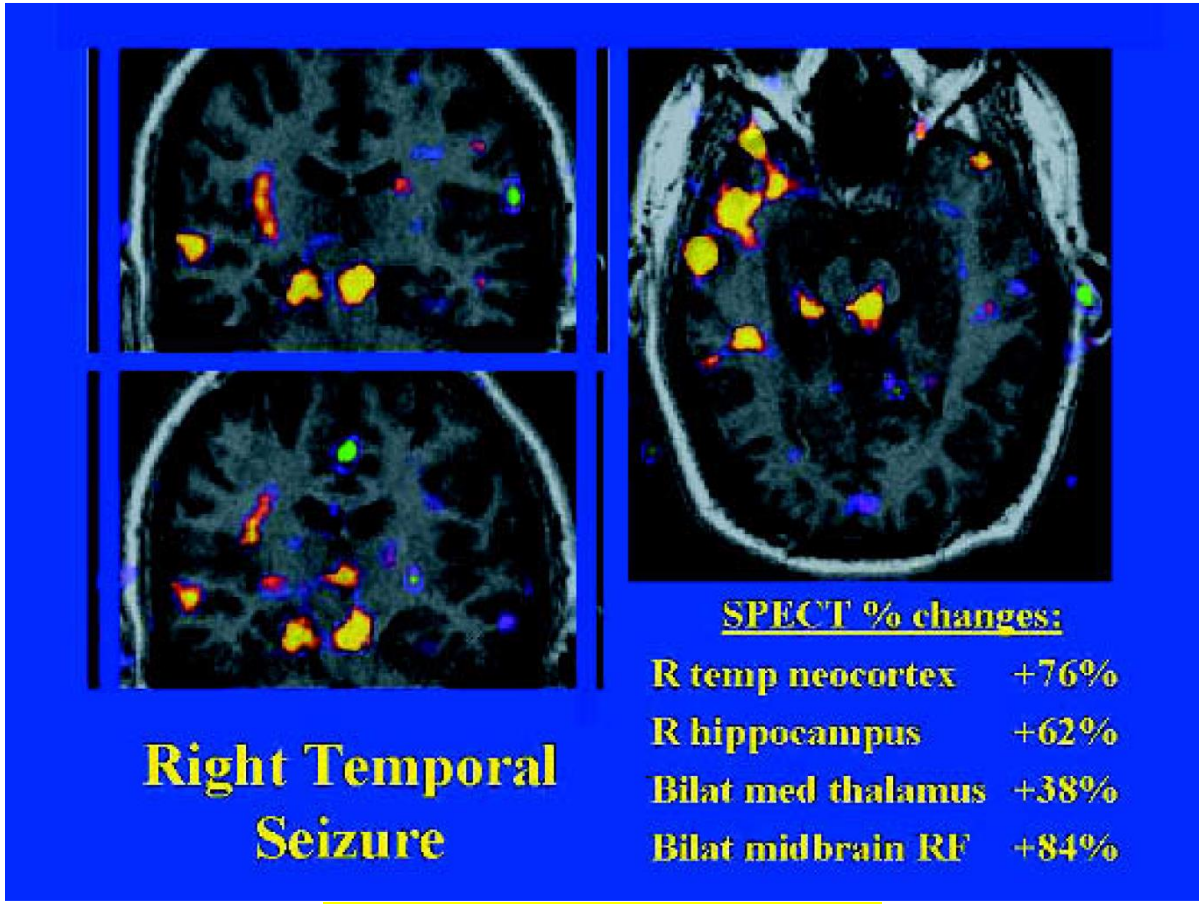
Epilepsy Network: PET



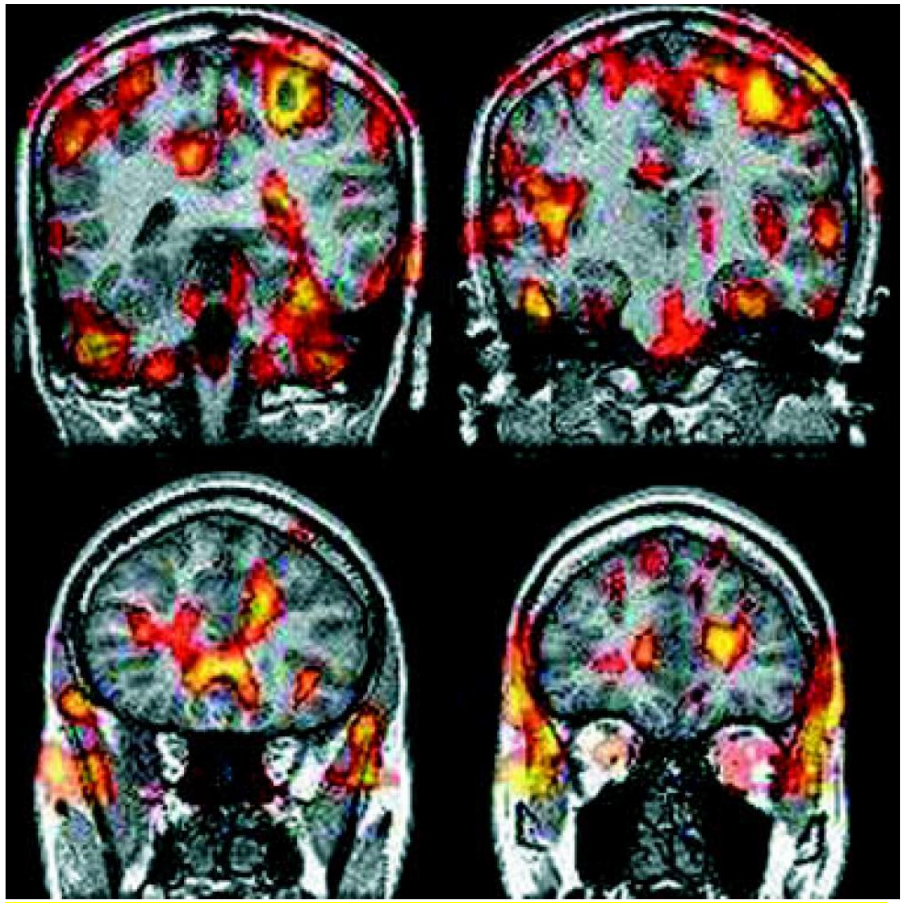
- Functional neuroimaging, specifically PET, can avoid the confounding influence of possible propagation.
- Difficulty in recording electrical changes in all areas, particulary subcortical structures (thalamus, basal gg.)
- The interictal hypometabolism in the areas in medial temporal/limbic network with a sensitivity 90%.
- Improvement in the hypometabolism observed preoperatively in ipsilateral inferior frontal lobe, the ipsilateral temporal neocortex, and both thalami

Spencer S. Epilepsia. 2002;43:219-27.

Epilepsy Network: SPECT



Temporal/limbic network



Superior parietal/medial frontal network

Spencer S. Epilepsia. 2002;43:219-27.

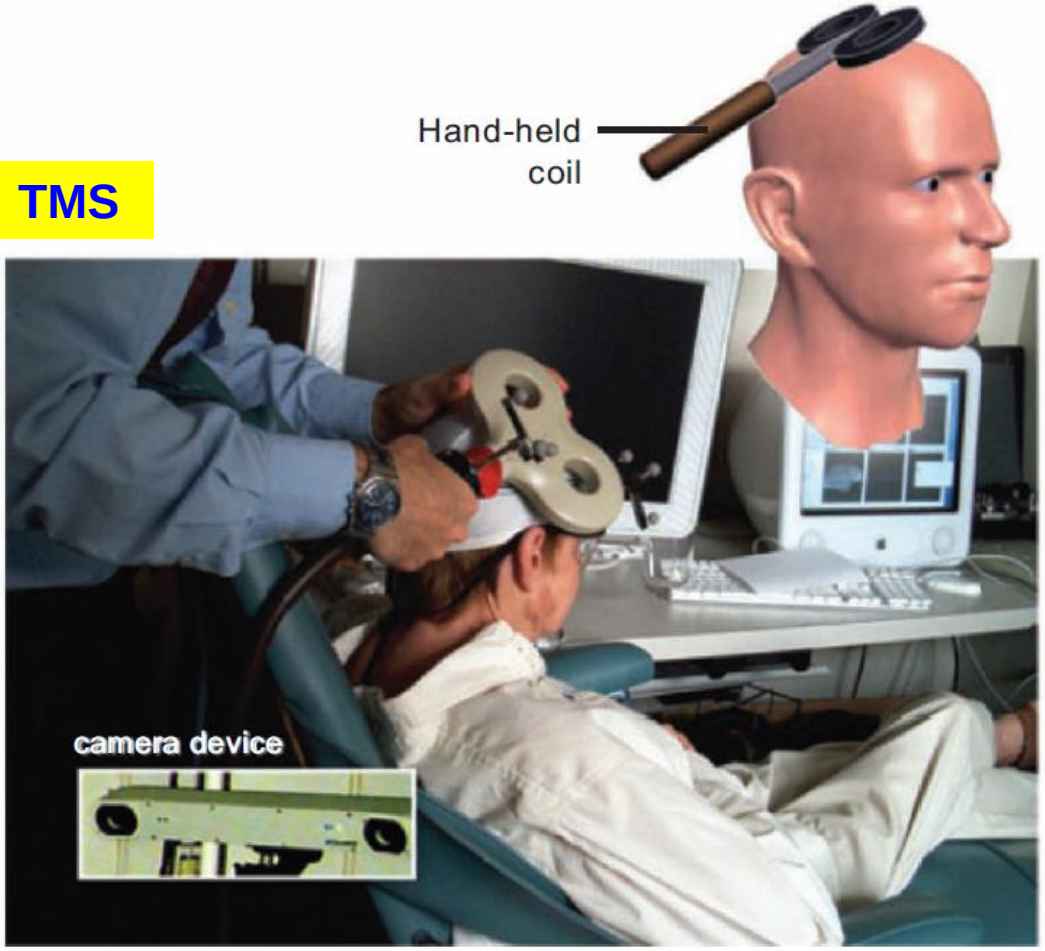
Epilepsy Network: Treatment/Outcome

- Response of intractable epilepsy to invasive therapy is a final line of evidence that supports the existence of human epilepsy networks.
- Medial temporal lobe epilepsy 60–90% excellent response. Procedures with no anatomical overlap are similarly successful.
- Disconnection (corpus callosotomy/multiple subpial transection) also targets an epilepsy network.
- "Nontargeted" electrical stimulation at subcortical structures (DBS, VNS, TMS, tDCS).

Spencer S. Epilepsia. 2002;43:219-27.

Epilepsy Network: Treatment/Outcome

TMS

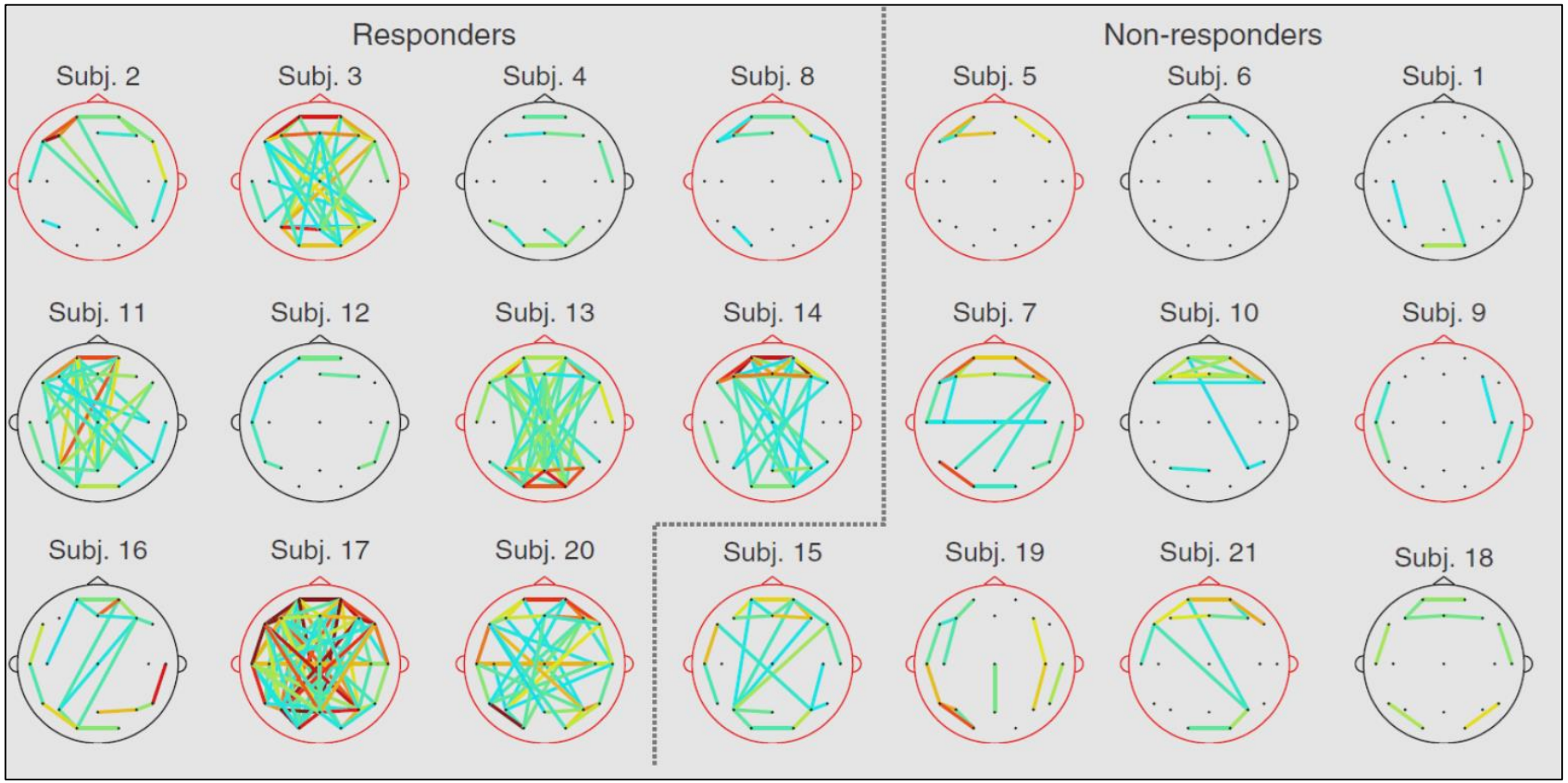


tDCS

Shafi M. Network Approaches to Diseases of the Brain. 2012;Chapter 8:100-123.

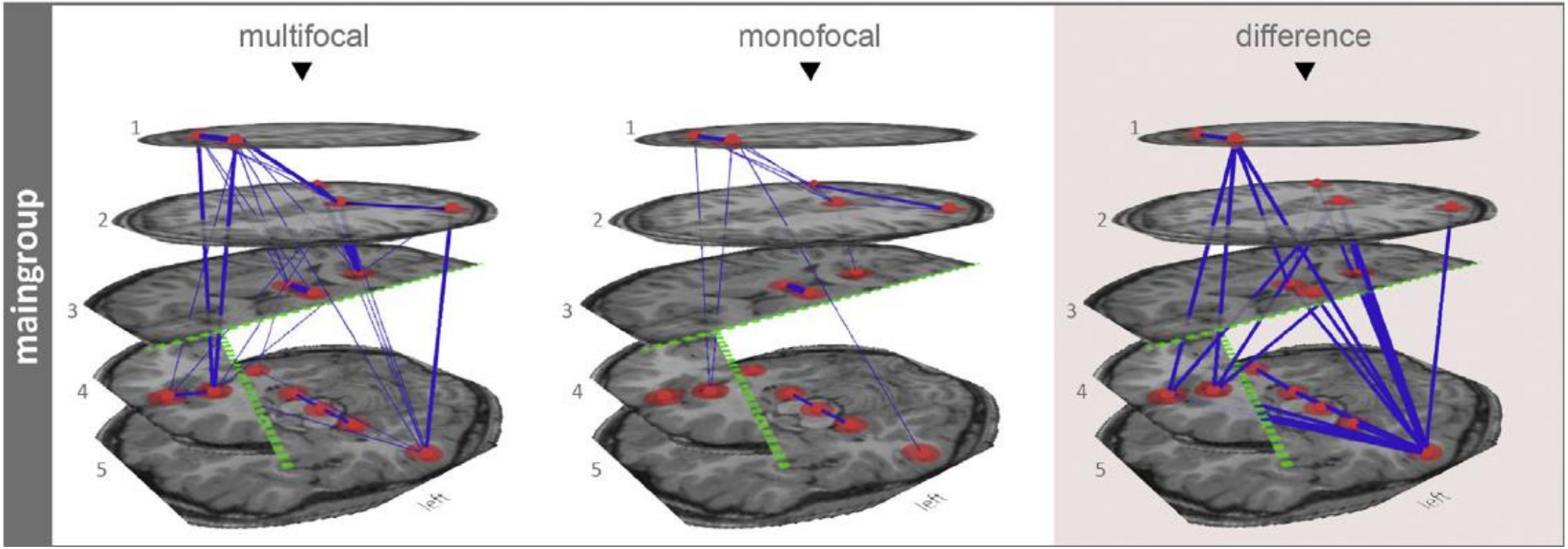
Pre-treatment functional connectivity maps for all epileptic spasms subjects

1. Changes in network connectivity and stability correlate to treatment response for ES.
2. Strong pre-treatment connectivity may predict favorable short-term treatment response.



Shrey D.W.et al. Clin Neurophysiol. 2018;129:2137-48.

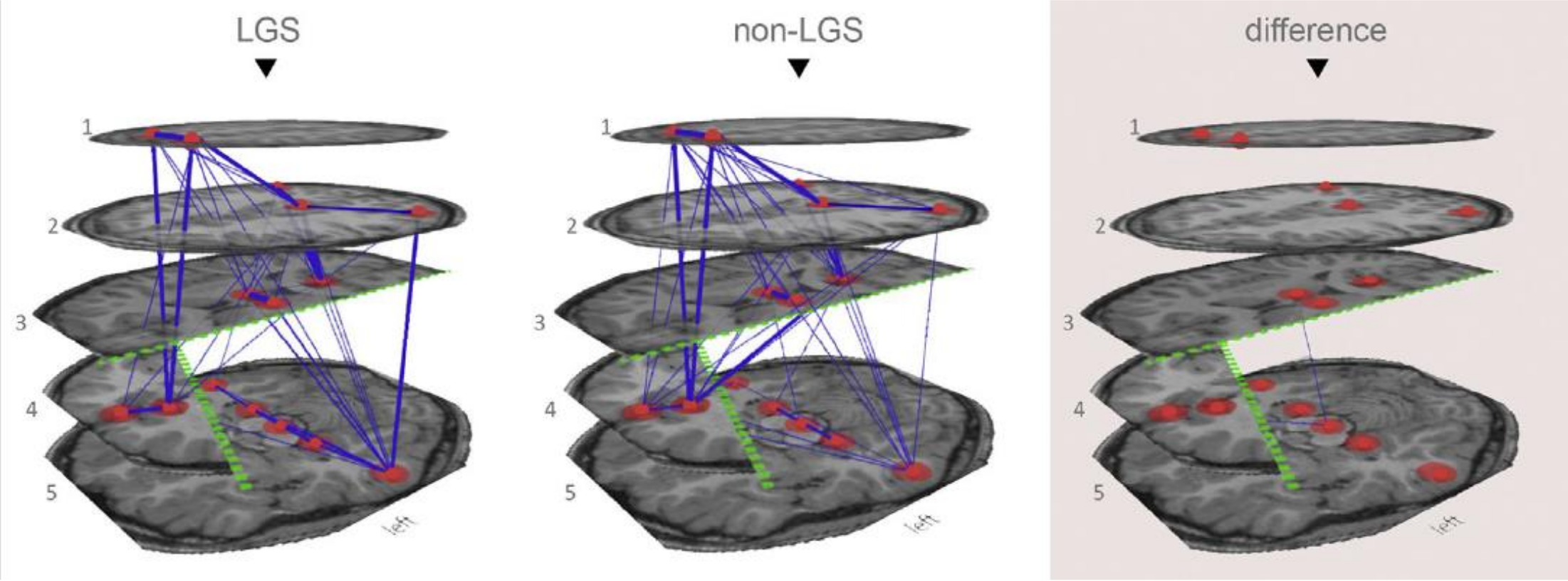
Multifocal epilepsy in children is associated with increased long-distance functional connectivity: An explorative EEG-fMRI study



33 children suffering from multifocal and monofocal (control group) epilepsies.

Siniatchkin M, et al. Eur J Paediatr Neurol. 2018;22:1054-65.

Multifocal epilepsy in children is associated with increased long-distance functional connectivity: An explorative EEG-fMRI study

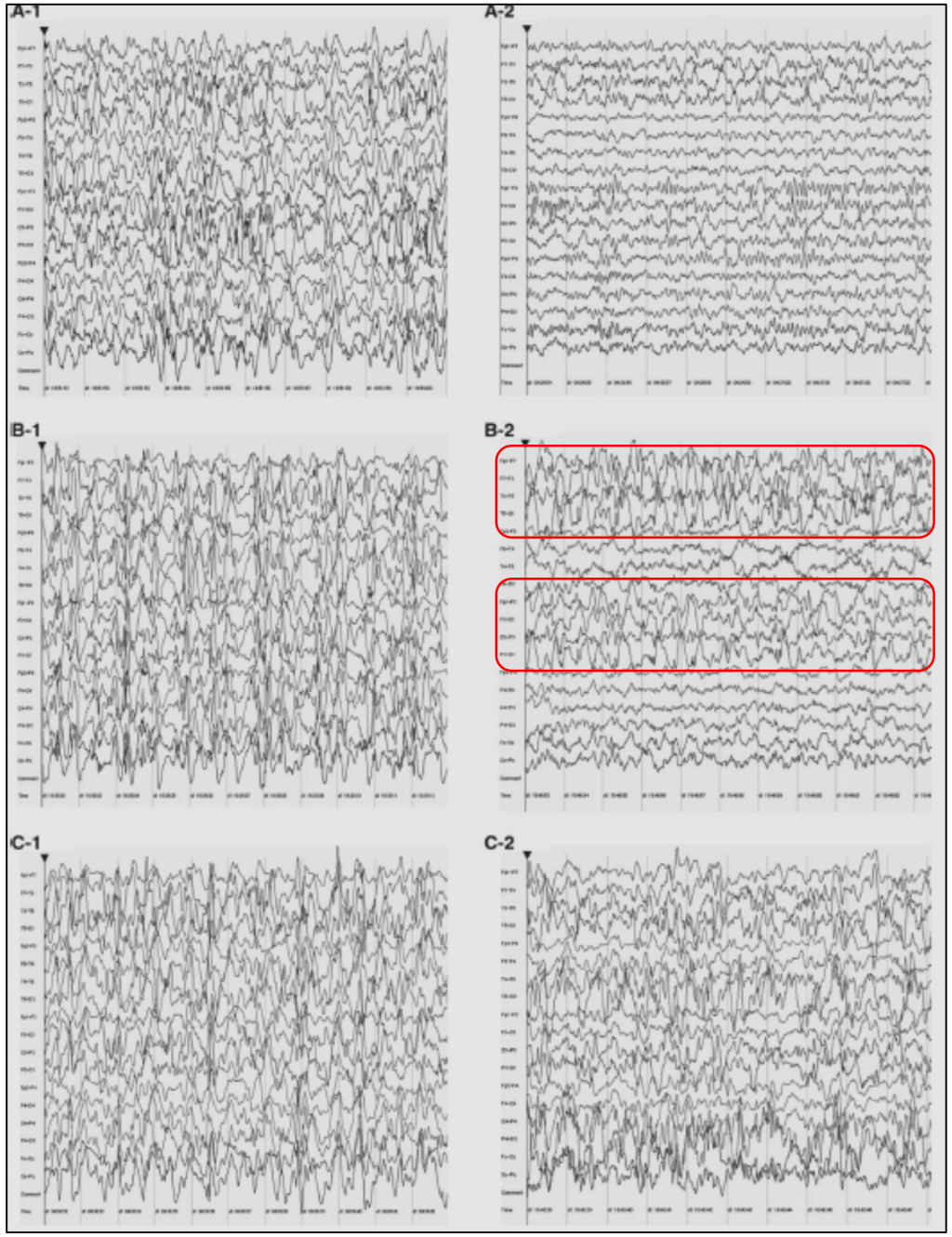


Siniatchkin M, et al. Eur J Paediatr Neurol. 2018;22:1054-65.

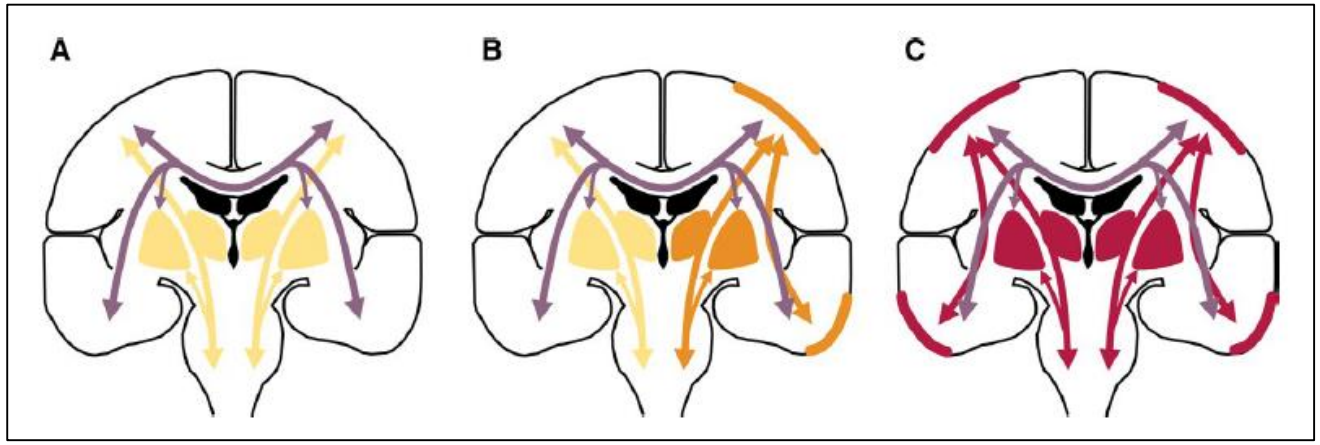
EEG before and after total corpus callosotomy for pharmacoresistant infantile spasms: Fast oscillations and slow-wave connectivity in hypsarrhythmia

- The increased power and connectivity of FOs in hypsarrhythmia may correlate with pharmacoresistant and surgically resistant seizures in IS.
- Modulation of the callosal system with subcortical/cortical epileptic discharges might play a role in generating hypsarrhythmia and IS.
- Prominent slow waves and connectivity without FOs might correlate with seizure freedom after total corpus callosotomy.

Otsubo H, et al. Epilepsia. 2019;60:1849-60.



EEG changes after total corpus callosotomy



Otsubo H, et al. Epilepsia. 2019;60:1849-60.

Take Home Message

- Structural, functional, and metabolic studies all demonstrate alterations in epileptogenic networks.
- Surgical failure indicates the disruption of the network is not enough to prevent it from generating seizures.
- Concept of epilepsy network may direct new approach of treatment for epilepsy.
  - Biomarkers to guide preoperative identification of surgical candidates
  - New nontargeted electrical stimulation
  - Surgical treatment in the region with least functional consequence but playing role in the network
  - Specific neurotransmitters in the regions of network
- Significant gains have been made in recent years about the epileptogenic network, but we are still far from using this information on the individual level and translate it into better patient outcomes.