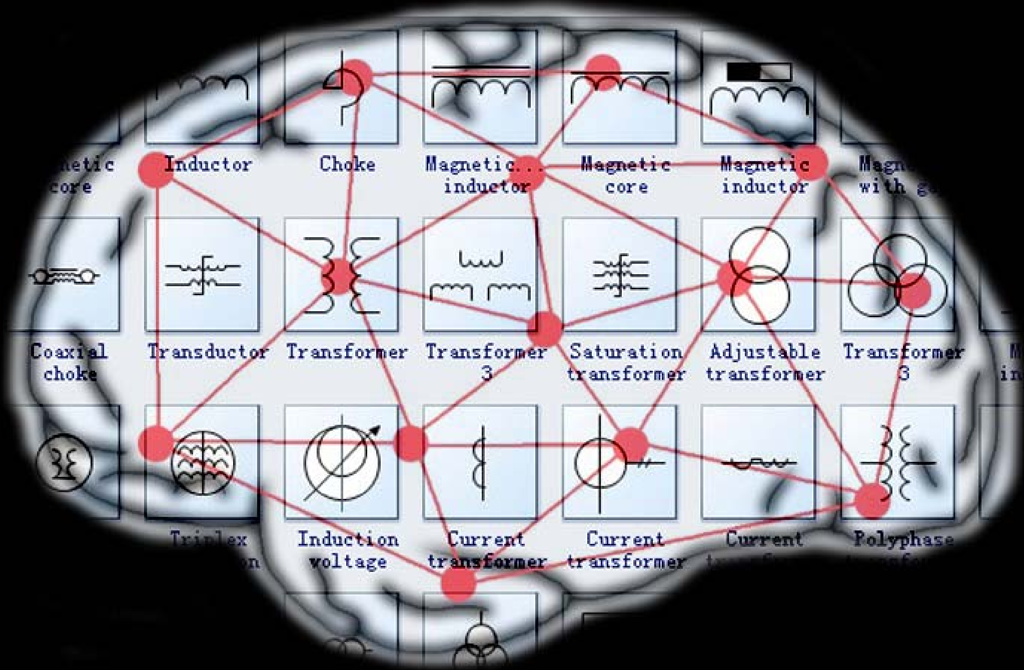
Controlling Brain Networks - Insights from Epilepsy

Klaus Lehnertz

and
many more



Dept. of Epileptology
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for Complex Systems

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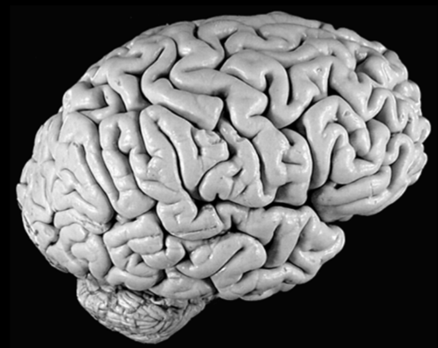
HISKP
Helmholtz-Institute
for Radiation- and
Nuclear Physics

Complex Network Brain

\# neurons: ~ 9×10^{10}
\# glia cells: ~ # neurons
\# synapses/neuron: ~ 10^3 - 10^4
length of all connections: ~ 10^7- 10^9 m
(~2.5 x distance earth-moon)
connectivity factor: ~ 10^{-6} (adult)
connectivity factor: ~ 10^{-4} (juvenile)
ion channels / neuron: ~ 10^2 - 10^3
neurotransmitter &
other active substances: ~ 50

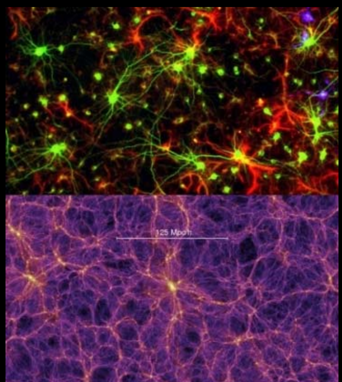
nonlinear
open
dissipative
adaptive



control; movement; perception; attention; learning; memory; knowledge; emotions; motivation; language; thinking; planning; personality; self-identity; consciousness; …; dysfunctions

structure ⟷ function

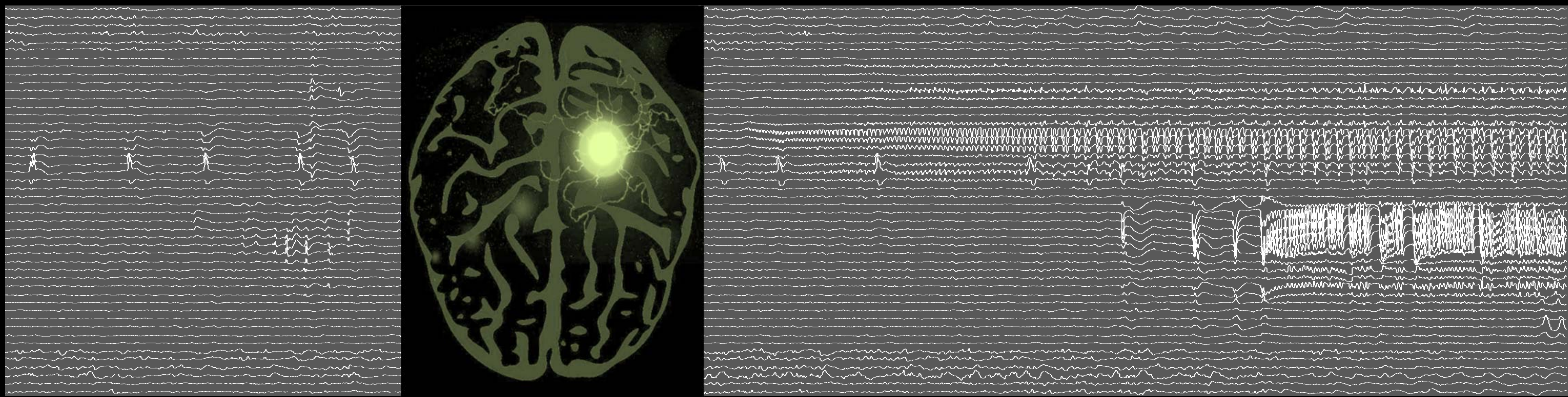
fluctuations
(endogenous/exogenous)
↓
order ⟷ disorder



Human Brain's Neuronal Network Has Similarities to Cosmic Web
(Vazza F and Feletti A. ***Front. Phys.*** 2020)

Some Facts about Epilepsy

Greek term for *seizure;* first mentioned ~ 1750 BC; **~ 1 % of world population***



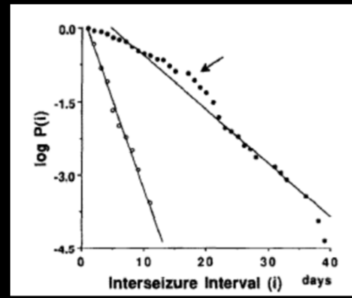
famous people suffering from epilepsy:

Sokrates, Alexander the Great, Julius Caesar, Lenin, Flaubert, Dostojevski, Carroll, Poe, Berlioz, Paganini, Händel, van Gogh, Newton, Pascal, Helmholtz, Nobel

** WHO fact sheet, June 2019*

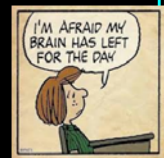
Extreme Event   Epileptic Seizure

- frequency: ~ 3 szrs/mon (max.: several 100 szrs/day)
- inter-seizure-intervals mostly Poissonian distributed



E Tauboll et al. **Epilepsy Res** 1991

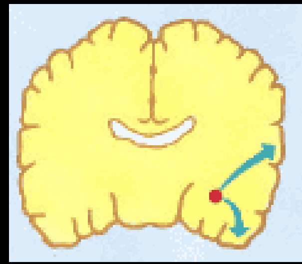
- (apparently) non-predictable (exception: reflex epilepsies)
- duration: 1 – 2 min (exception: status epilepticus > 5 min)
- during the seizure: impaired mental functions, altered consciousness, loss of consciousness, involuntary movements, …



- after the seizure: neurologic dysfunctions, depression, …
- main seizure types:

  generalized seizure (apparently instantaneous)
  focal seizure (with/without generalization)

Epileptic Focus vs. Epileptic Network

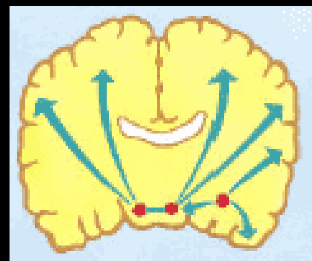


traditional concept: ***epileptic focus***

- circumscribed area of the brain
- critical amount of neurons → epileptic seizures

novel concept: ***epileptic network***

- functionally and anatomically connected brain structures
- activity in any one part affects activity in all the others
- vulnerability to seizures in any one part of the network influenced by activity everywhere else in the network
- seizures may entrain large neural networks from any given part
- growing evidence from imaging, electrophysiological, and modeling studies

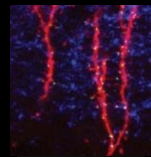
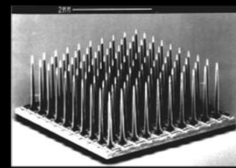
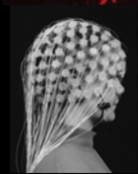


*e.g. S. S. Spencer, **Epilepsia**, 43, 219, 2002*
*T. Berg & I. E. Scheffer, **Epilepsia**, 52, 1058, 2011*
*KL et al., **Physica D** 267, 7, 2014*

Complex Networks and Epilepsy

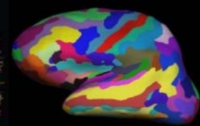
paradigm shift: from *epileptic focus* to *epileptic network*

local scale (hard (impossible?) to access):
vertices → neurons
edges → synapses

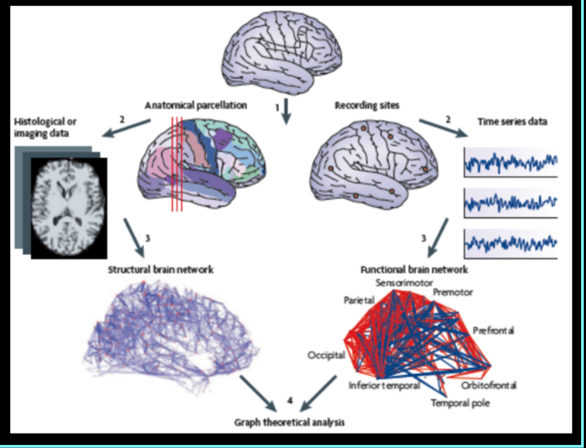





medium/large scale
vertices → sensors (dynamics of networks of neuron networks)
edges → interactions (binary, weighted, directed)





evolving brain network
- time series analysis (strength/direction of interactions)
- time-dependent global/local network characteristics
  (clustering coefficient, average shortest path length,
  synchronizability, assortativity, centrality, etc.)



hot topics
- seizure precursor in epileptic brain network (where, when, how)
- controlling epileptic brain network

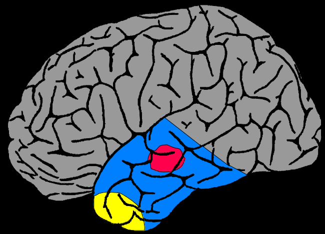
KL et al., ***Physica D*** *2014*

E Bullmore & O Sporns, ***Nat Rev Neurosci*** *2009*

Current Approaches to Control Epilepsy (Seizures)

antiepileptic drugs; success*: ~ **70 %**
side effects, long-term treatment

epilepsy surgery; success: **~ 60 %** (15 % – 85 %)
long-term outcome, surgery-induced alterations?



neurostimulation*;* success: ~ **50 %**
side effects, long-term outcome?

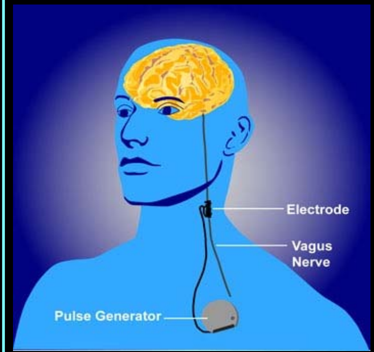
← great hopes

behavioral interventions, self management*;*
success: < **20 % (?)**
rare, no reliable conclusions so far

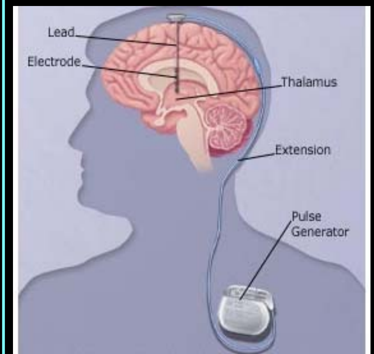
* reduction in seizure frequency

Neurostimulation Approaches to Control Epilepsy

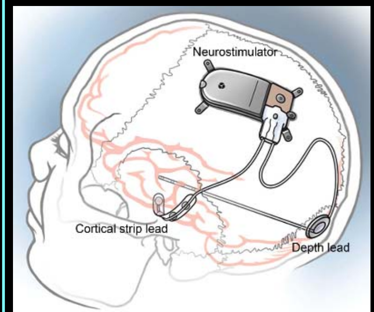
idea: modulate brain states using "targeted" stimulation



invasive Vagal Nerve Stimulator (iVNS)
global unspecific brain stimulation via vagal nerve
szr reduction: ~35 % (1 yr) to ~43% (3 yrs)



Deep Brain Stimulator (DBS)
scheduled stimulation of thalamus (*network hub*)
szr reduction: ~41 % (1 yr) to ~56% (2 yrs)



Responsive Neurostimulator (RNS)
stimulation of epileptic focus (foci) @szr detection
szr reduction: ~44 % (1 yr) to ~53% (2 yrs)
to 48-66 % (3-6 yrs)

mechanism of action not fully understood

devices not (yet) coupled to seizure prediction systems !

efficiency comparable to drug treatment

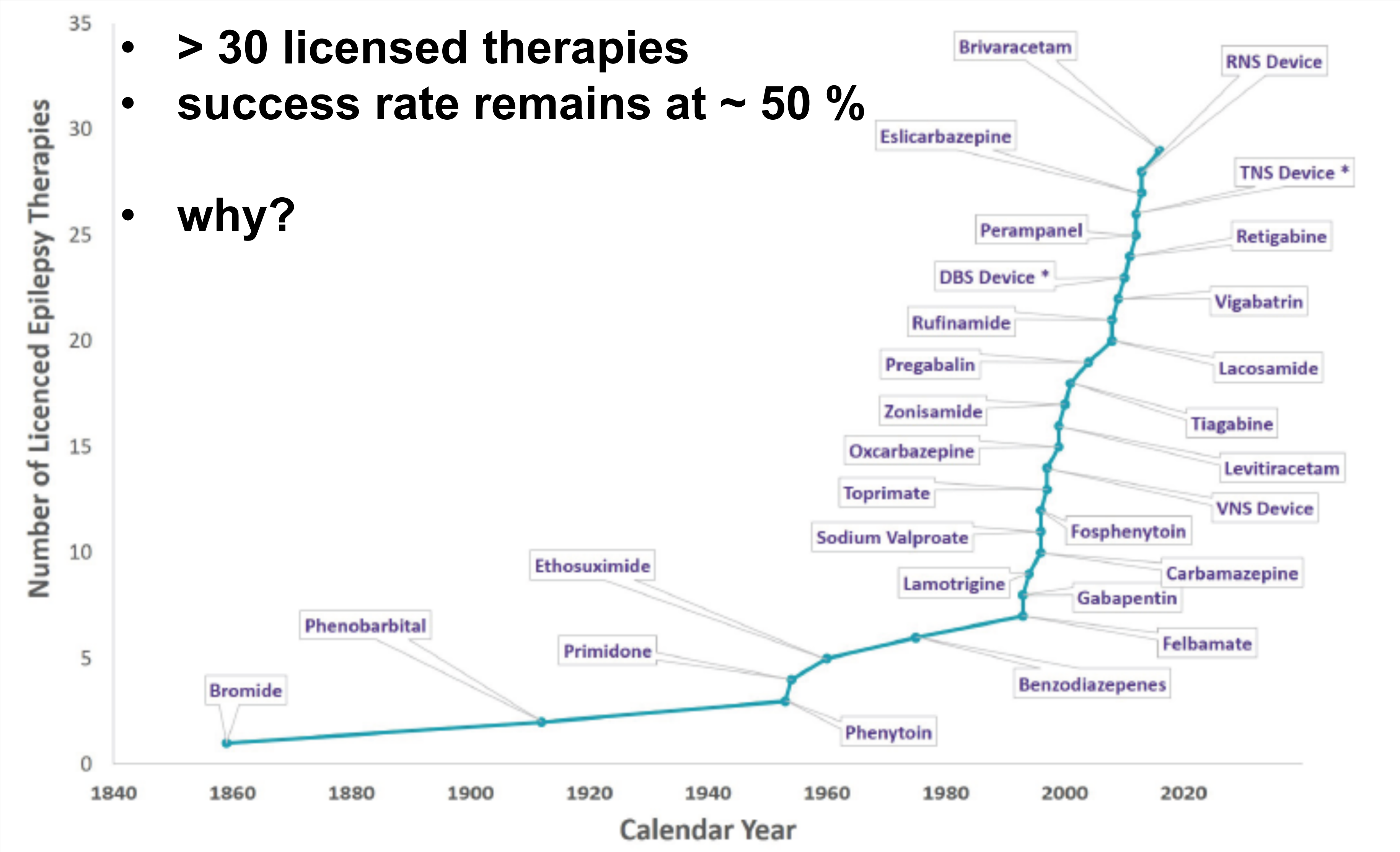
mostly targeting epileptic focus !

Ryvlin et al., ***Lancet Neurol*** 2021

Current Approaches to Control Epilepsy (Seizures)

- > 30 licensed therapies
- success rate remains at ~ 50 %

- why?



Neurostimulation Approaches to Control Epilepsy

possible limiting factors

- invasive systems: life time of battery, risk of infection, …
- stimulation parameters (often heuristically derived)
- restrictions related to approval from regulatory authorities
- suitability of outcome measure(s)

- mostly targeting single nodes in the epileptic brain network (except VNS → global activation?)
- mostly targeting pathological dynamics (seizure, spikes, …)

Why Not Use Network Control Techniques?

REVIEWS OF MODERN PHYSICS, VOLUME 88, JULY–SEPTEMBER 2016

Control principles of complex systems

Yang-Yu Liu

Channing Division of Network Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115, USA and Center for Cancer Systems Biology, Dana-Farber Cancer Institute, Boston, Massachusetts 02115, USA

Albert-László Barabási

Center for Complex Network Research and Departments of Physics, Computer Science and Biology, Northeastern University, Boston, Massachusetts 02115, USA, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115, USA, and Center for Network Science, Central European University, Budapest 1052, Hungary

REVIEWS OF MODERN PHYSICS, VOLUME 90, JULY–SEPTEMBER 2018

Colloquium: Control of dynamics in brain networks

Evelyn Tang

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REVIEWS

318 | MAY 2019 | VOLUME 1 www.nature.com/natrevphys

The physics of brain network structure, function and control

Christopher W. Lynn[1] *and Danielle S. Bassett*[1,2,3,4,5 *]

NeuroImage 176 (2018) 83–91

Contents lists available at ScienceDirect

NeuroImage

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

Warnings and caveats in brain controllability

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NeuroImage 200 (2019) 552–555

Contents lists available at ScienceDirect

NeuroImage

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

Brain controllability: Not a slam dunk yet

Samir Suweis[a,b,*], Chengyi Tu[c,d], Rodrigo P. Rocha[b,e,f], Sandro Zampieri[b,g], Marzo Zorzi[h,i], Maurizio Corbetta[b,j,k]

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Why Not Use Network Control Techniques?

current problems and limitations

- linear vs nonlinear
- targets structure only; structure-function relationship?
- limitations in measuring brain network structure (e.g. DTI)
- data-driven identification of driver nodes/regions/modules
- desired state? (not synchronized!)
- minimum control energy for clinical applications?
- concepts applicable in clinical setting?
- …

Recent Developments to Control Epilepsy

noninvasive brain stimulation (NIBS) techniques

and God said
$$\oint \vec{E}\cdot d\vec{a} = \frac{q_{enc}}{\varepsilon_0}$$
$$\oint \vec{E}\cdot d\vec{l} = -\int \frac{\partial \vec{B}}{\partial t}\cdot d\vec{a}$$
$$\oint \vec{B}\cdot d\vec{a} = 0$$
$$\oint \vec{B}\cdot d\vec{l} = \mu_0 I_{enc} + \mu_0\varepsilon_0 \int \frac{\partial \vec{E}}{\partial t}$$
and then
there was *LIGHT*

transcranial magnetic stim. | **NIBS** | transcranial electric stim.

tMS
single pulse
paired pulse
regular repetitive
patterned
…

transcranial
ultrasound
tUS

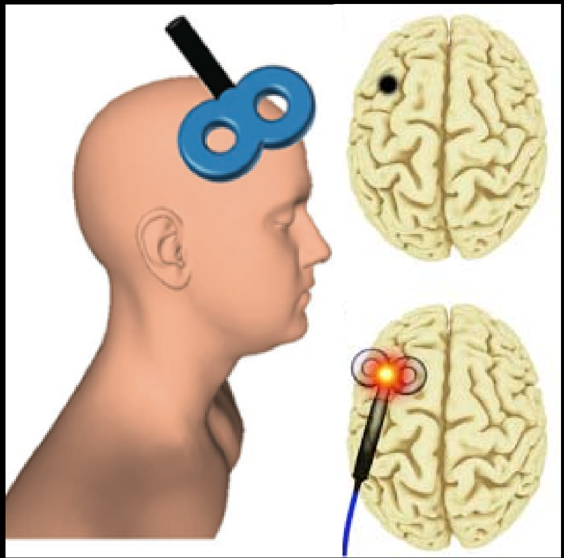
tES
direct current
alternating current
random noise
…

nerve stimulation

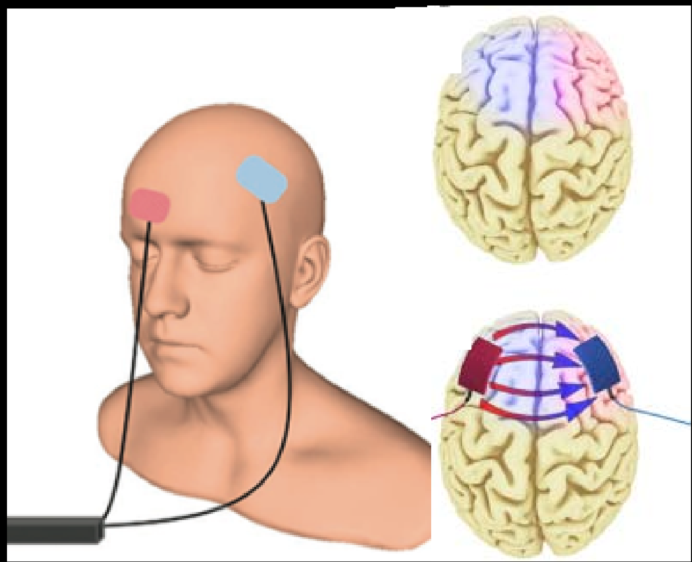
Recent Developments to Control Epilepsy

noninvasive brain stimulation (NIBS) techniques

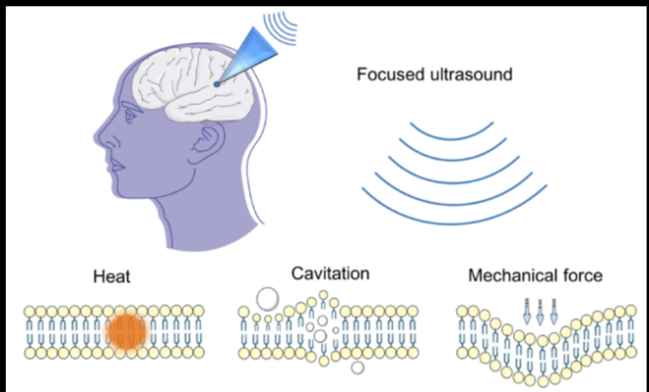
tMS



tES



nVNS



tUS

+ wide applicability:
from diseases to cognitive enhancement

Dayan et al., ***Nat. Neurosci.*** *2013; Sale et al.,* ***Neurosci. Biobehav. Rev.****, 2015*

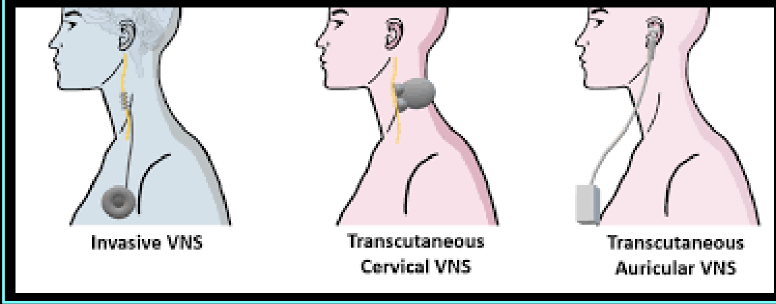
Towards Controlling Evolving Epileptic Network

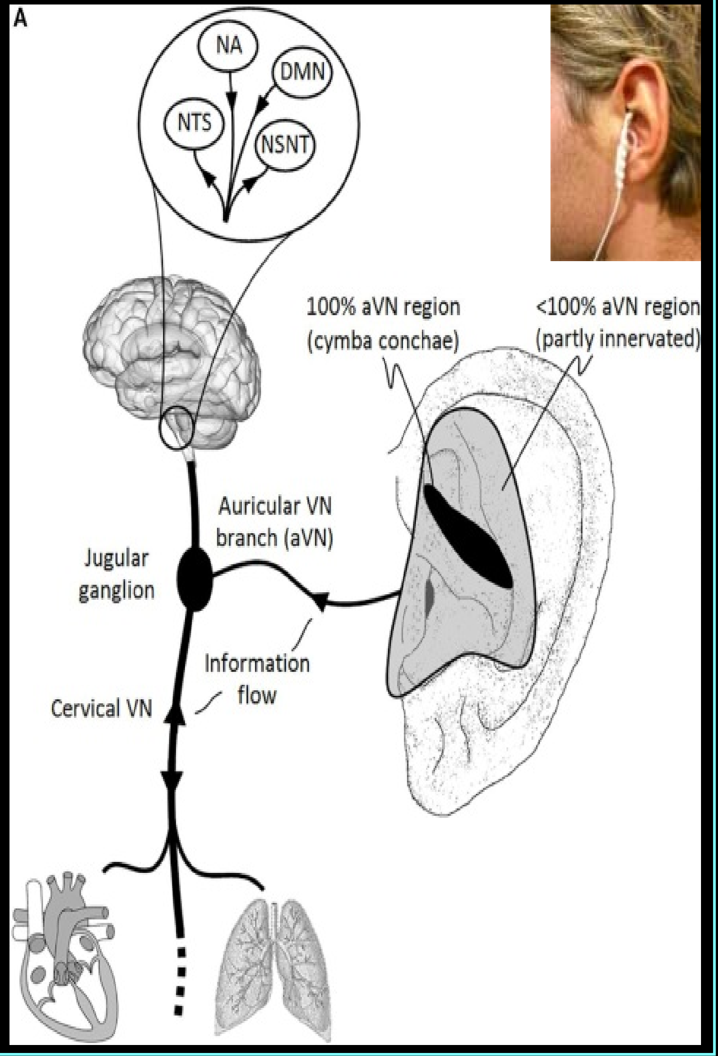
transcutaneous auricular Vagus Nerve Stimulation (taVNS)

- novel ***noninvasive*** ansatz*
- stimulation via auricular branch of VN
- mimics neurophysiological effects of iVNS

- broad applicability (various diseases +++)
- epilepsy: szr reduction: ~60 % (1 yr)**
  (3 stims/day for an hour, indiv. adj. stim. intens.)

- mechanism of action ?
- optimum stimulation parameter?
- impact on evolving epileptic brain network ?

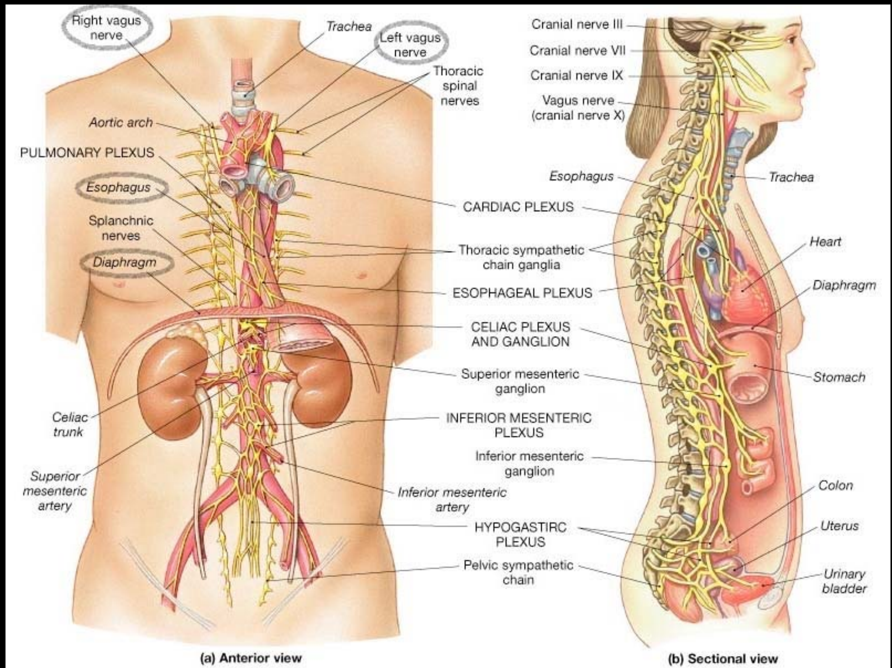




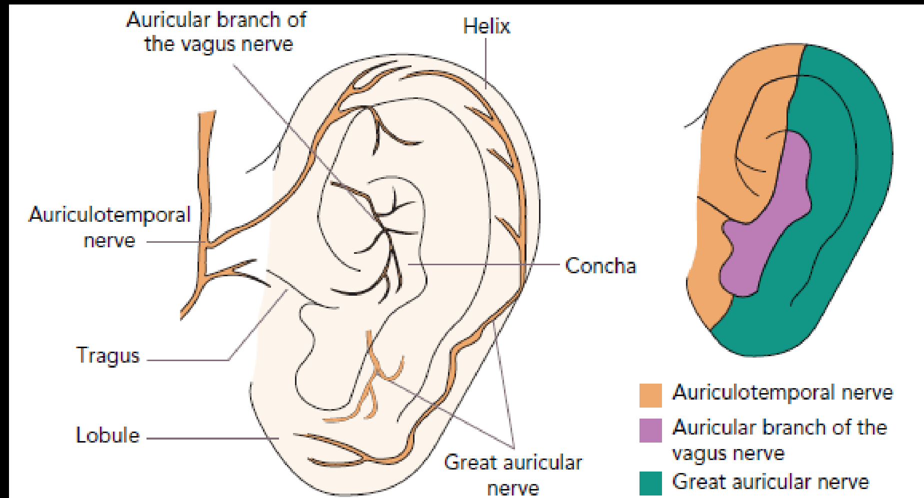
* *concept proposed in 2000; first proof of concept in epilepsy Stefan et al., ***Epilepsia*** *2012*
** *von Wrede & Surges,* ***Autonom. Neurosci.****, 2021*

Short Intermezzo: Vagus Nerve – Great Wanderer

- *vagus* Latin for 'wandering'; 10th cranial nerve (CN X)
- longest nerve of autonomic system (brain ↔ intestine)
- 20% efferent and 80% afferent fibers; bidirectional



involved in regulation of autonomic, immune, cardiovascular, gastrointestinal, respiratory and endocrine systems



Jiang et al., ***Arrhyth & Electrophysiol. Rev.***. 2020

external ear is the only location where the vagus sends its peripheral branch (auricular nerve; aVN)

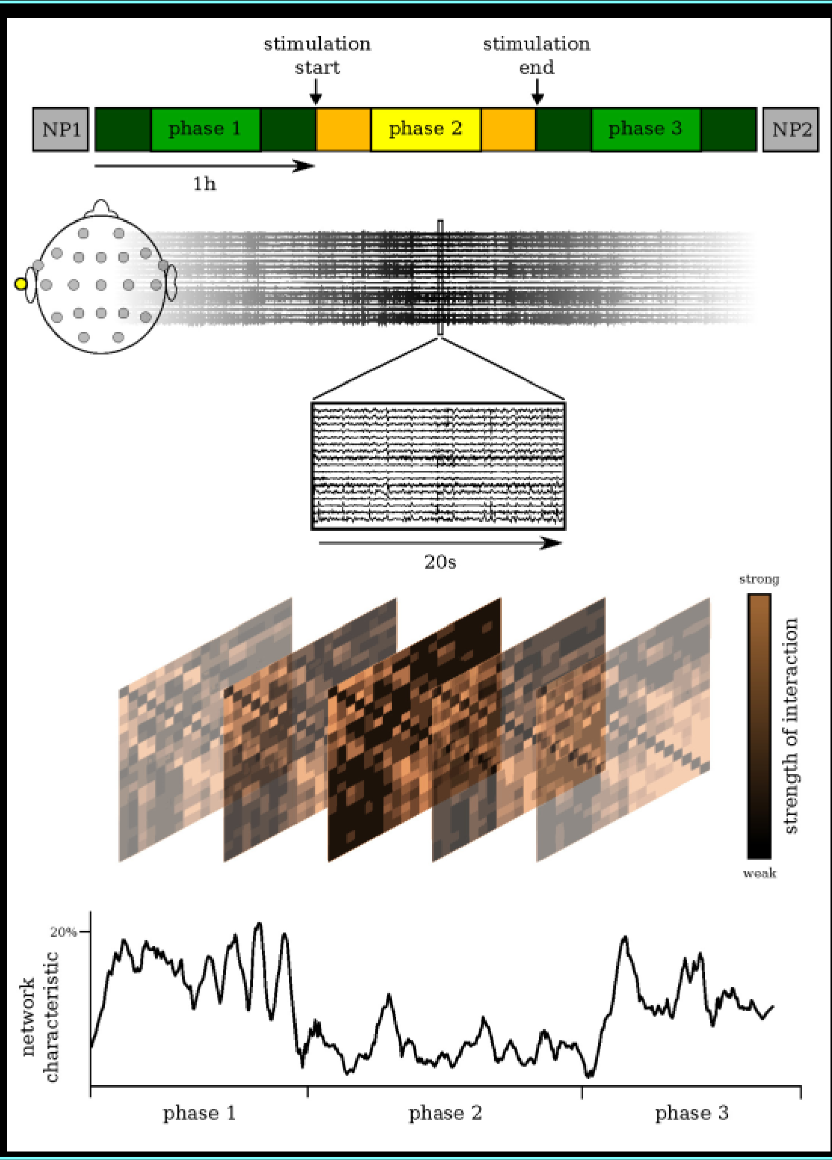
→ ***external gateway to brain***

e.g. Kaniusas et al, ***Front. Neurosci.*** *2019; Butt et al.,* ***J. Anat.*** *2020; Goggins et al.,* ***Clin. Sci.*** *.2022*

Towards Controlling Evolving Epileptic Network

transcutaneous auricular
Vagus Nerve Stimulation (taVNS)

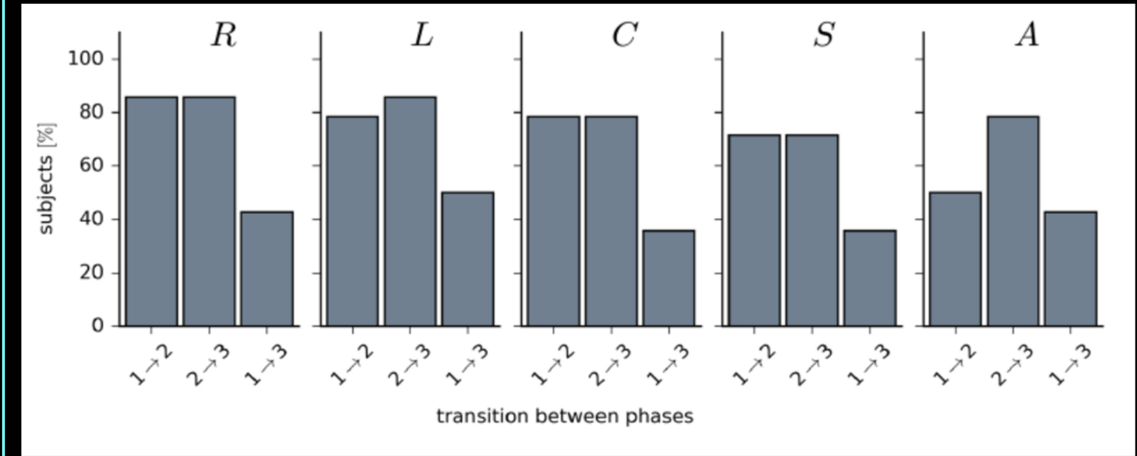
- 30 subjects w/ disorders of CNS
- 3 h scalp EEG recording; afternoon
- individually adjusted stimulation parameter (biphasic signal form, duration: 20 s, pause 30 s, frequency 25 Hz; pulse intensity adjusted individually (raised slowly until the subject noticed a “tingling”, but no pain)
- neuropsychological testing before/after stimulation
- weighted evolving brain networks (mean phase coherence)
- time-resolved global network characteristics (average shortest path length *L*, global clustering coefficient *C*, assortativity *A*, synchronisability *S*)
- time-resolved local network characteristics (various vertex/edge centralities)

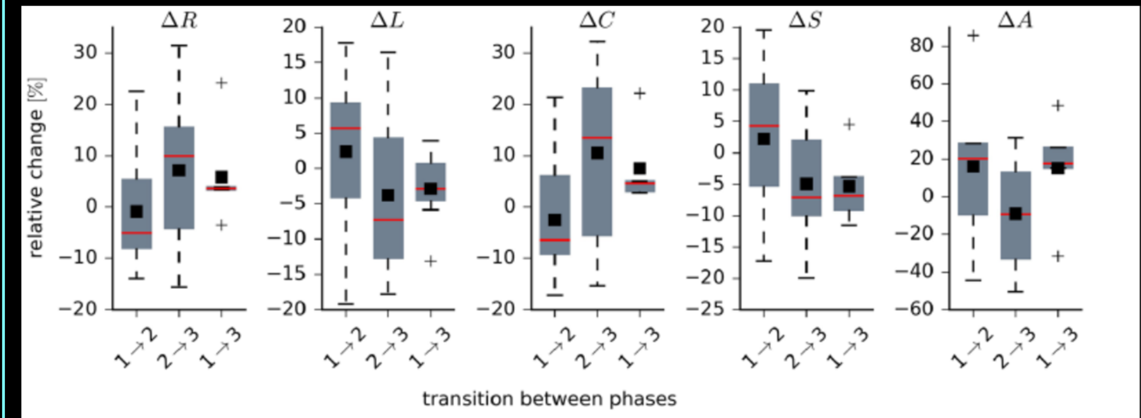


*R von Wrede et al., **Sci. Rep**. 2021; T Rings et al. **Front. Physiol.** 2021; R von Wrede et al., **Front. Hum. Neurosci**, 2022*

Towards Controlling Evolving Epileptic Network

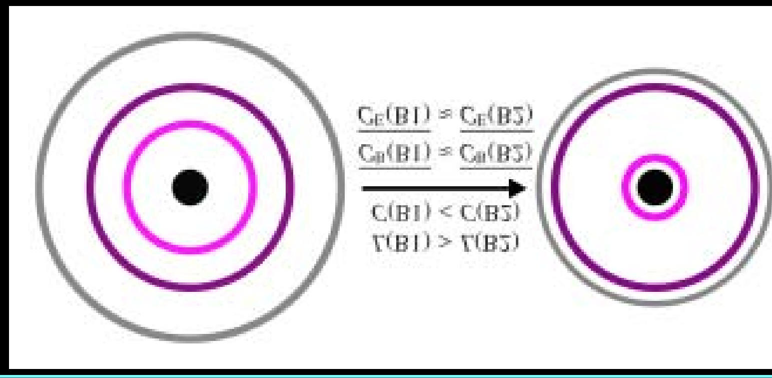
transcutaneous auricular Vagus Nerve Stimulation (taVNS) - I





immediate effect of stimulation:

- modifies topology (network reconfiguration)
- enhances network robustness and stability
- importance structure (vertices/ edges) unchanged
- "stretching" and "compression" of network (model: *breather*)



R von Wrede et al., **Sci. Rep**. 2021; T Rings et al. **Front. Physiol.** 2021; R von Wrede et al., **Front. Hum. Neurosci**, 2022

Towards Controlling Evolving Epileptic Network

transcutaneous auricular Vagus Nerve Stimulation (taVNS) - I

differential impact on different epilepsy types (focal/generalized vs contr.)

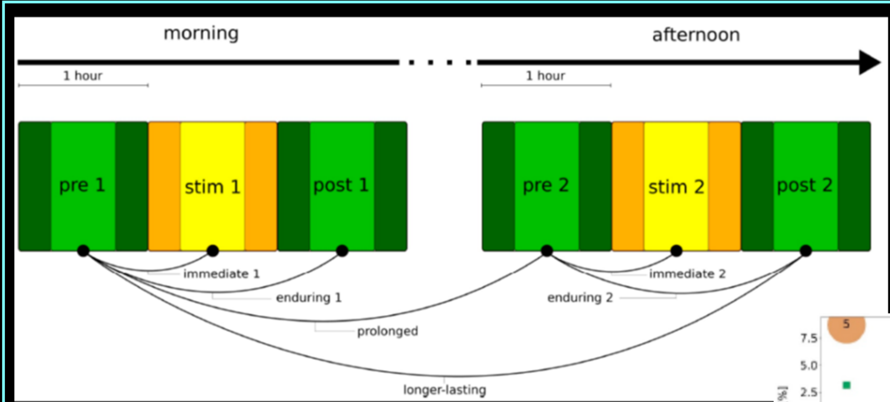
TABLE 1 | Synopsis of taVNS-induced immediate and enduring modifications of global and local characteristics of weighted fully connected functional brain networks in different epilepsy types.

		Focal epilepsy group	Generalized epilepsy group	Non-epilepsy group
Global network scale				
Topology	Immediate effect	Segregation ↑ integration ↓	Segregation ↓ integration ↑	Segregation ↑ integration ↔
	Enduring effect	Segregation ↓ integration ↑	Segregation ↑ integration ↓	Segregation ↓ integration ↑
Robustness	Immediate effect	↑	↑	↑↑
	Enduring effect	↑↑	↓↓	↑↑
Stability of the synchronized state	Immediate effect	↔	↑	↑
	Enduring effect	↑	↓	↔
Local network scale				
Path-based centrality index	Vertices	Diffuse	Diffuse	Diffuse
	Edges	Diffuse	Diffuse	Diffuse
Interaction-strength-based centrality index	Vertices	Diffuse	Diffuse	Diffuse
	Edges	Diffuse	Diffuse	Diffuse

↑, *increase;* ↑↑, *strong increase;* ↓, *decrease,* ↓↓, *strong decrease;* ↔, *negligible change.*

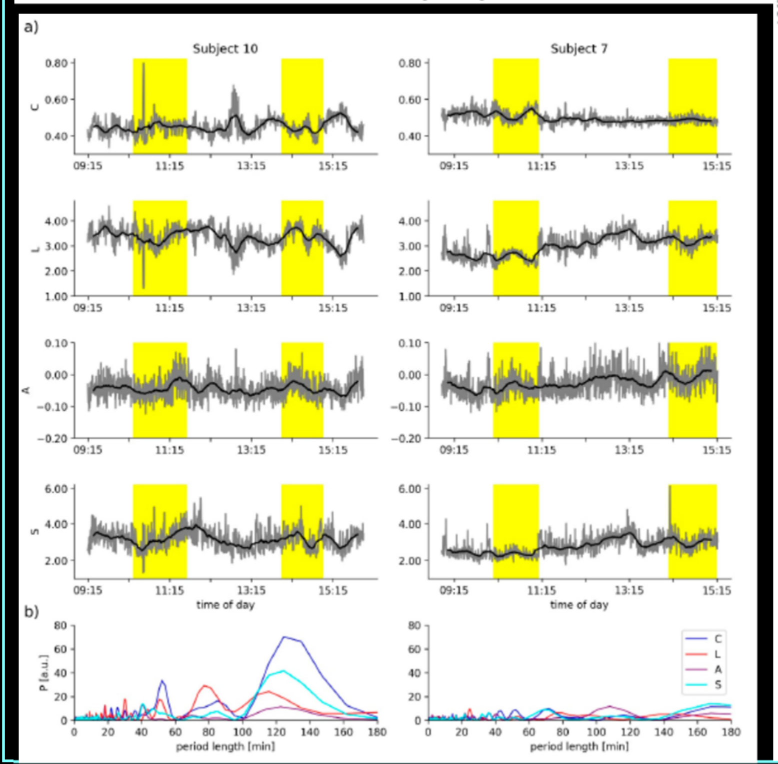
R von Wrede et al., ***Front. Hum. Neurosci****, 2022*

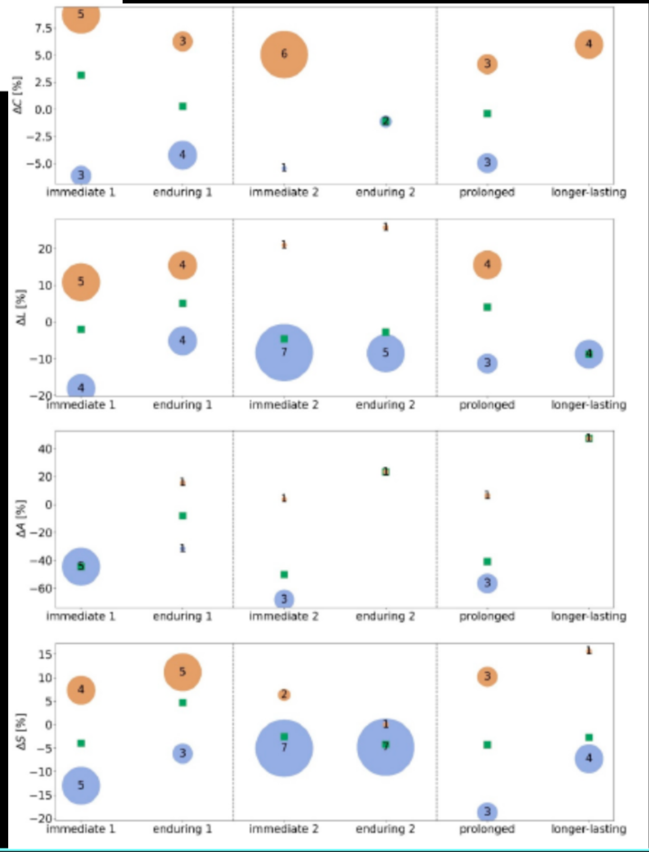
Towards Controlling Evolving Epileptic Network



transcutaneous auricular Vagus Nerve Stimulation (taVNS) - II

- 15 subjects with epilepsy
- continuous EEG recording
- two 1 h stim phases (morning / afternoon)

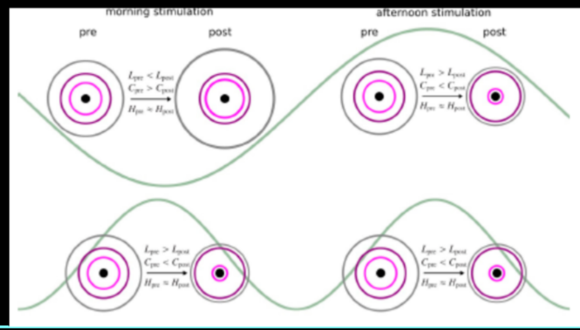




stimulation-induced network alterations: afternoon >> morning

topology and stability

strong diurnal influences!



R von Wrede et al., ***Brain Sci.*** *2022*

Towards Controlling Evolving Epileptic Network

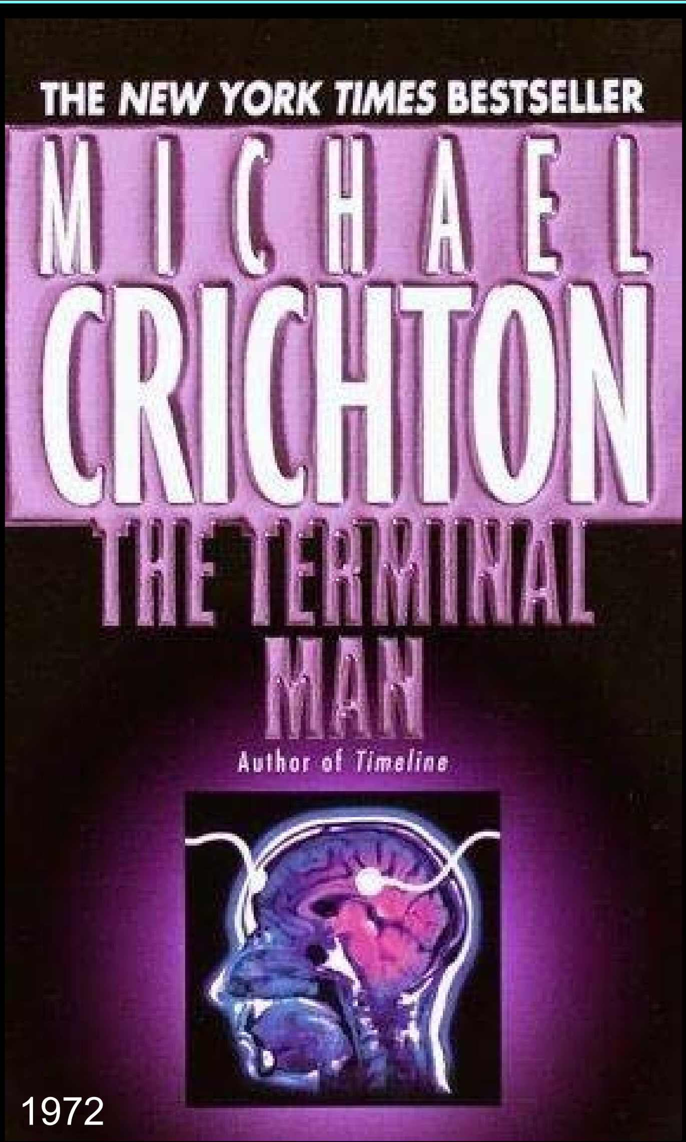
transcutaneous auricular Vagus Nerve Stimulation (taVNS)

taVNS promising *neuromodulation* technique
- targets the evolving large-scale epileptic network (global modification)
- modifications → healthy brain network (long-term effect?)
- possible mechanism of action:
  re-activate impaired/lost vagal sensory feedback to the brain
- patient: easy-to-handle, good usability

requires revisions
- outcome measure(s)
- optimal stimulation parameter
- application recommendations

long-term studies (underway)

Towards Controlling Evolving Epileptic Network

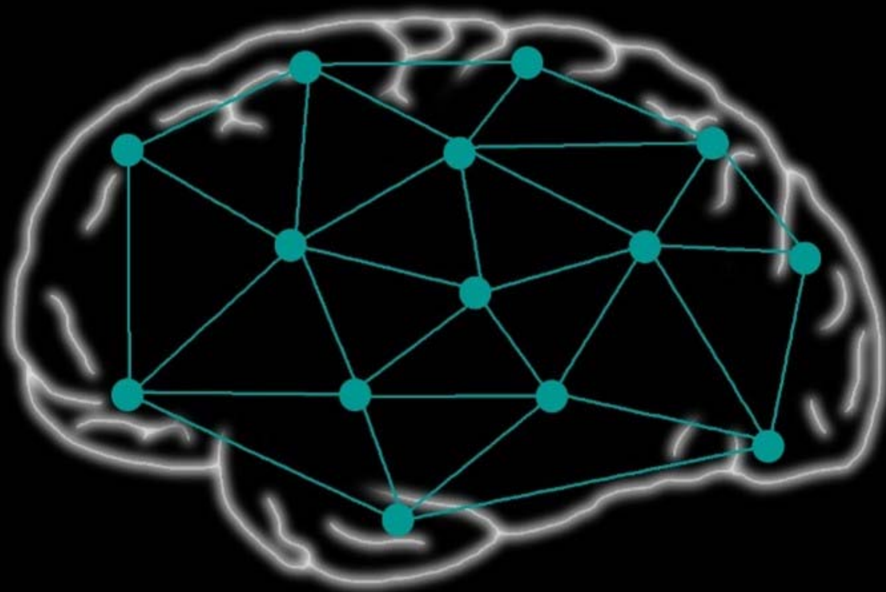


1972

nonlinear, open, dissipative

adaptive

plasticity



can the epileptic brain be controlled?

(or: does it want to be controlled?)