Brain-Heart-Lung Communication: An organomics approach to complex disorders

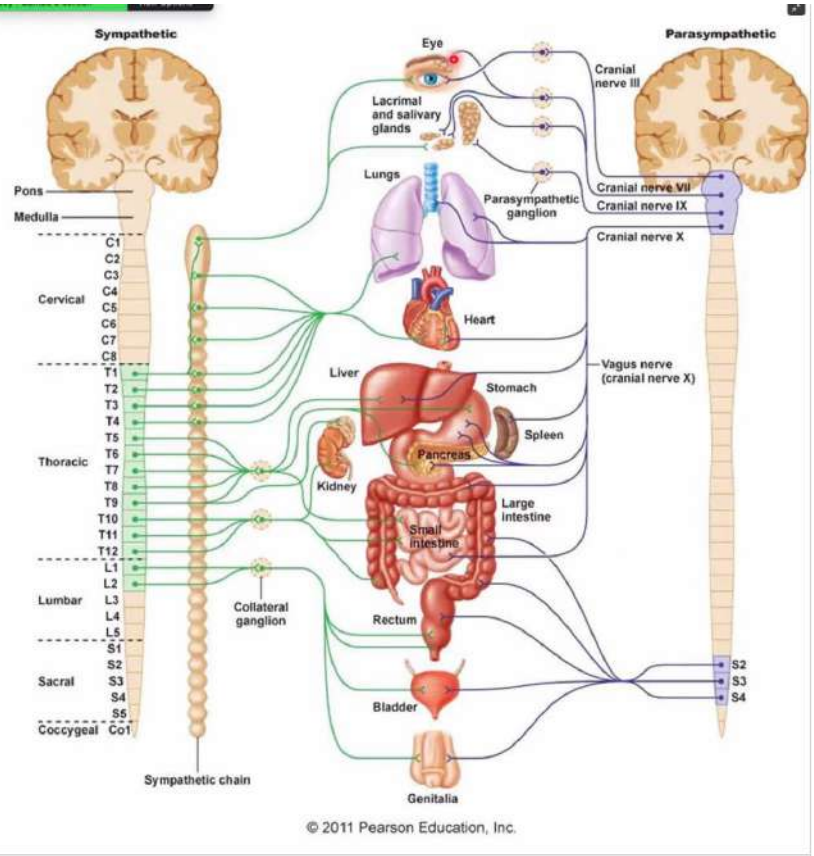
A. Bezerianos[1], G. Dimitrakopoulos[2], L. Iasemidis[1,3]

[1]Dept. of Translational Neuroscience, Barrow Neurological Institute, Phoenix, AZ,USA, [2]Dept. of Informatics, Ionian University, Corfu, GR, [3]Dept. of Biomedical Engineering, Arizona State University, Tempe, AZ, USA.

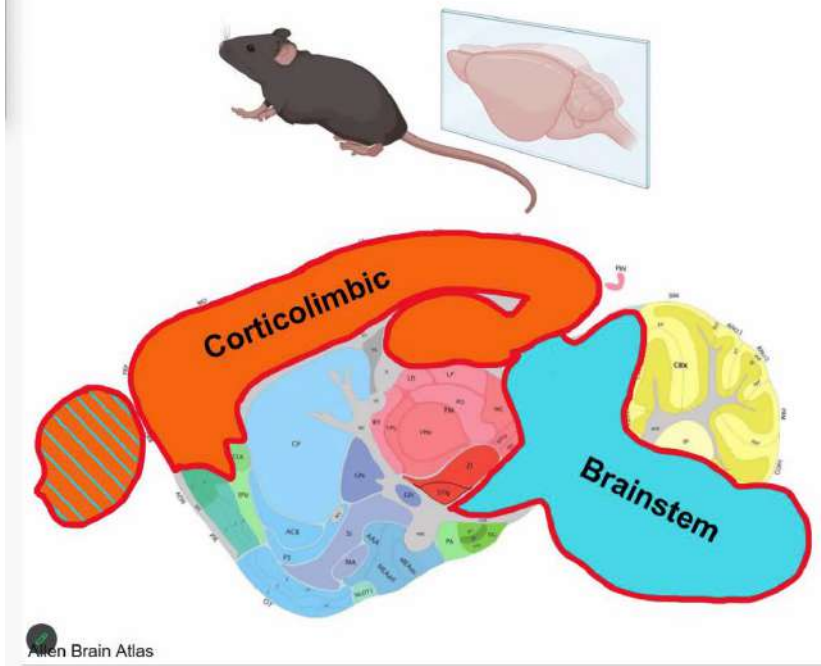
A. Brain - Heart - Lung Communication

Autonomic Nervous System (ANS)

- 3 branches:
  - sympathetic, parasympathetic, enteric
- Master regulator of heart and lungs
- Upstream influences in the limbic system
  - hippocampus, amygdala



Mapping neuronal populations contributing to SUDEP

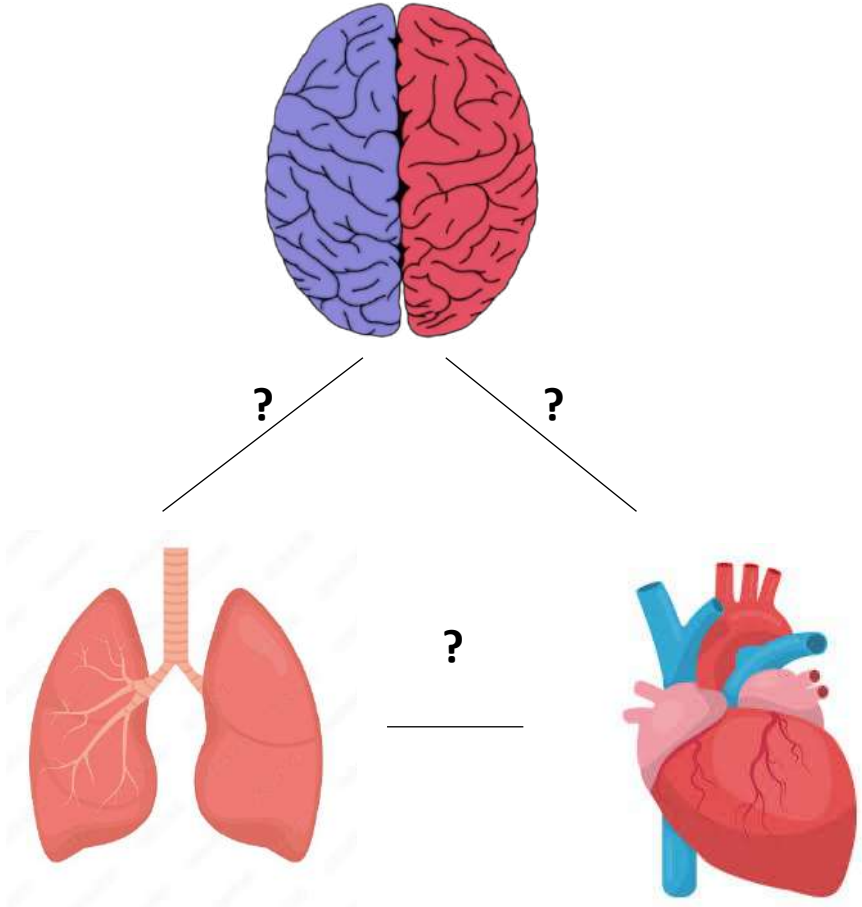


What are the critical neuronal subpopulations?

What are the events that happen in SUDEP?

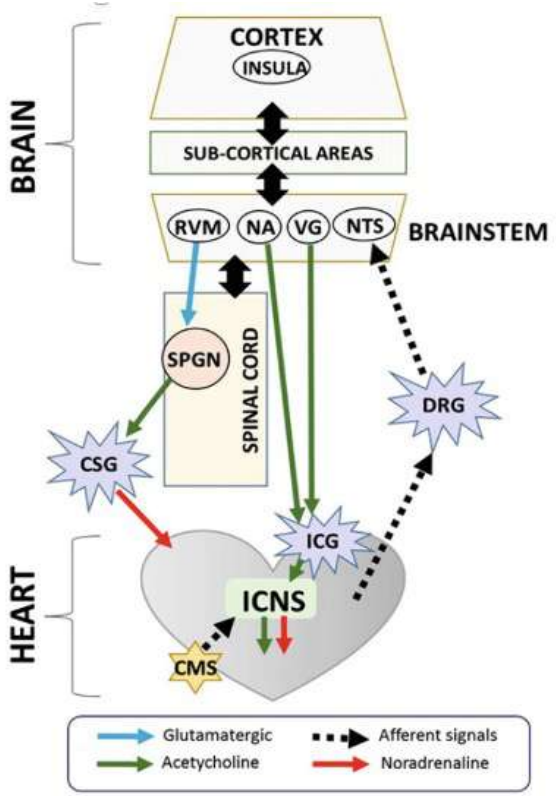
Sudden Unexpected Death in Epilepsy (SUDEP)

- SUDEP poses a significant risk to life expectancy for individuals with epilepsy.
- Mechanistic insight, while incomplete, has advanced through clinical observational studies and animal models.
- We still lack preventative therapies, which will depend on understanding SUDEP mechanisms.
- Recurrent convulsive seizures are the major SUDEP risk factor.
- Cardiorespiratory dysfunction precedes SUDEP, but whether cardiac arrhythmias are major proximate culprits for SUDEP remains to be determined.

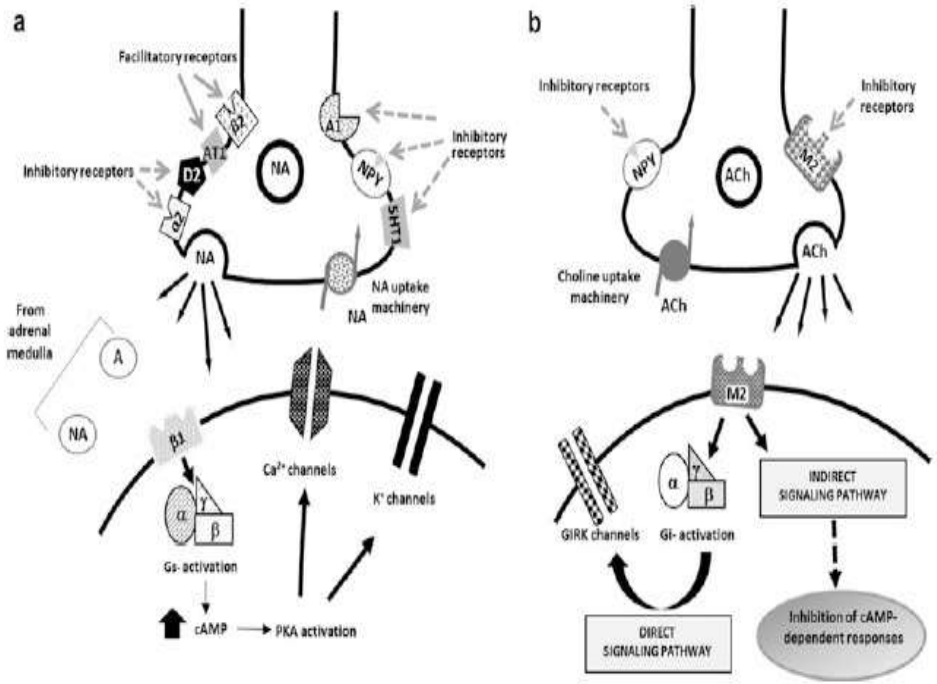


I. BRAIN - HEART Communication

The Hardware



The Software

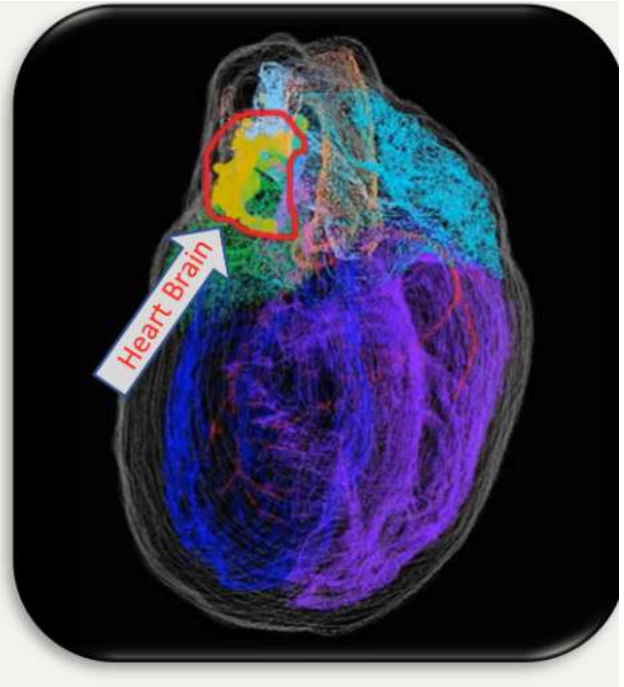


Sympathetic and Parasympathetic branches of ANS

BRAIN - HEART Communication

The challenges

What is underestimated and less researched is the role of the heart's little brain



Point of interest:
1. Different organization between male and female

The Problem

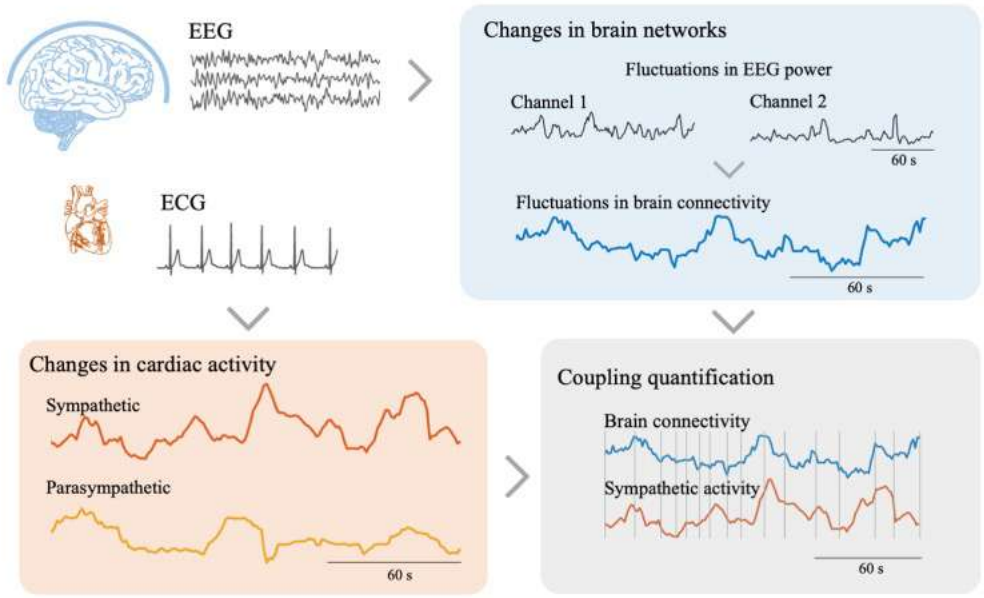
How the transport of hormones, neurotransmitters and ions is reflected in the electrical signals recorded in the heart (ECG) and brain (EEG) and their correlations.

The answer (electrical)

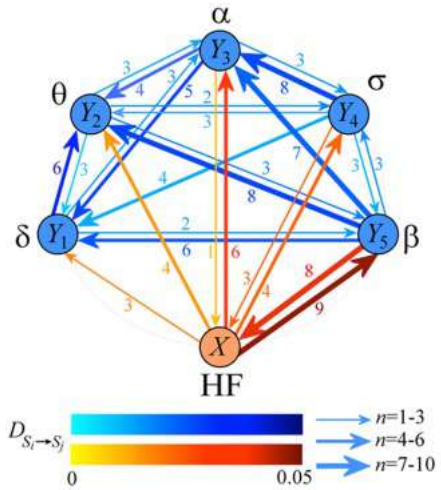
Local properties (EEG and/or EKG) and their directed coherence (e.g. GPDC, dPLI) and their mapping via complex networks models

BRAIN - HEART Communication

The coupling between brain connectivity and Heartbeats dynamics



Information dynamics of brain heart network



BRAIN - HEART Communication in SUDEP

The challenge

During focal, multifocal or generalized epileptic seizures, to calculate the moment when the brain's control of the heart leads it to abnormal function and to block it, leaving the "little brain" to control the heart.

The answer

Local properties (EEG and/or EKG) and their directed coherence (e.g. GPDC, dPLI) and their mapping via complex networks models.

II. BRAIN - LUNG Communication

Overview

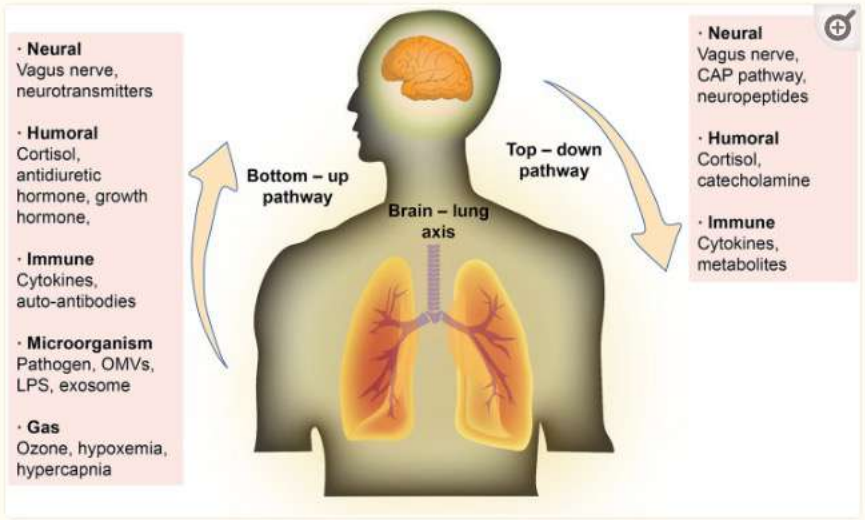


Fig. 5

The total bidirectional pathways in brain–lung axis. Overall, the brain regulates the lung via neuroanatomical, humoral, immune and metabolic pathways. The lung influences the brain primarily via humoral, immune, pathogenic microorganisms and metabolic pathways. *CAP* cholinergic anti-inflammatory pathway, *LPS* lipopolysaccharide, *OMVs* outer membrane vesicles

Details

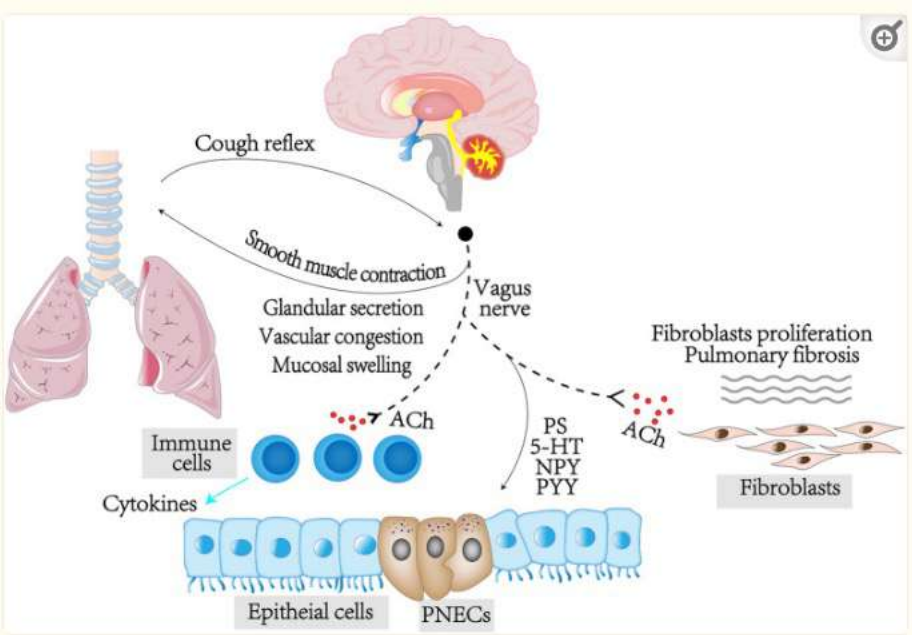


Fig. 1

Vagus nerve could regulate bronchial smooth muscle contraction, glandular secretion, vascular congestion, and mucosal swelling in lung, while it could accept the stimulation from lung. Furthermore, vagus nerve releases acetylcholine (ACh), acting on ACh receptors, α7nAChR, of immune cells, which is the CAP. Pulmonary neuroendocrine cells, which are controlled by vagus nerve, secret neuroendocrine factors that regulate the physiological function of lung. 5-*HT* 5-hydroxytryptamine, *NPY* neuropeptide Y, *PNECs* pulmonary neuroendocrine cells, *PS* substance P, *PYY* peptide YY

BRAIN - LUNG Communication

The challenge

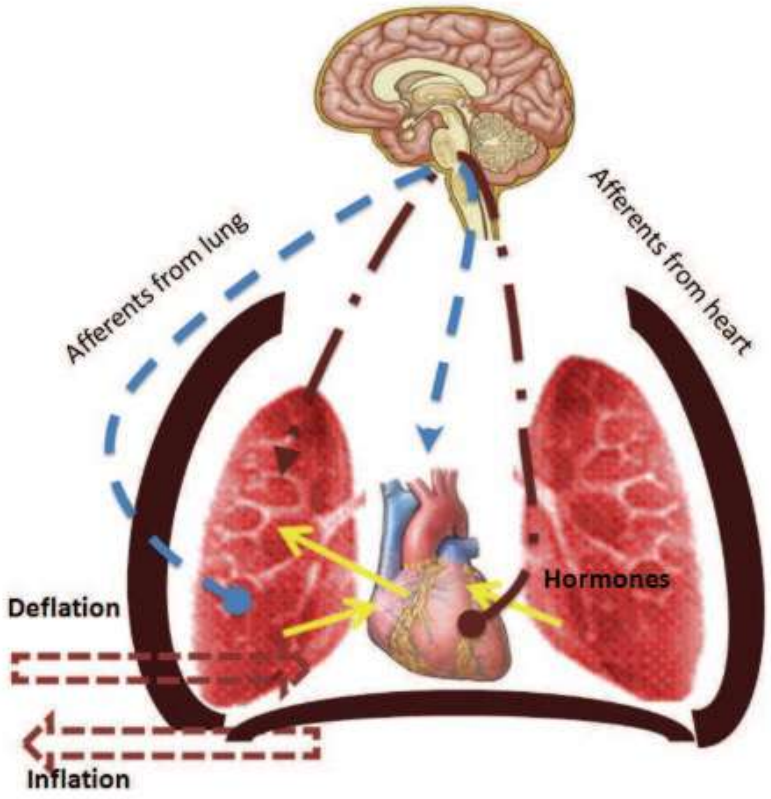
During focal, multifocal or generalized epileptic seizures, it is essential to calculate the moment when the brain stops sending signals for the contraction of the lung muscles that control the movement of the lungs.

The answer

External pacemaker will periodically stimulate contraction of lung muscles.

III. HEART - LUNG Communication

Overview



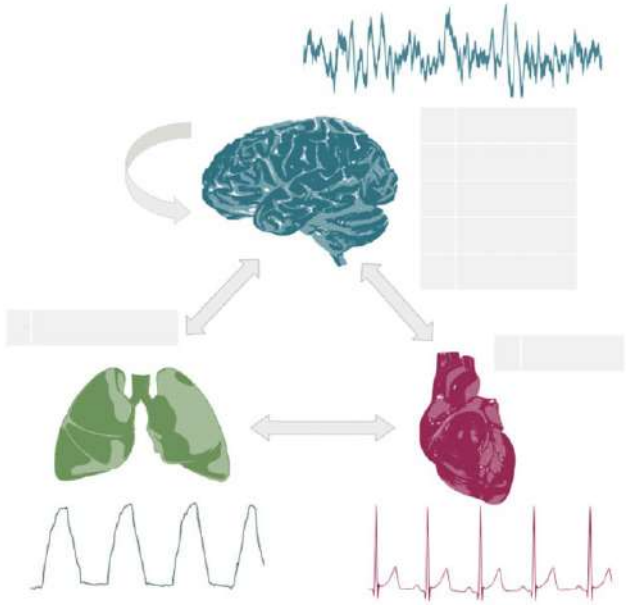
The heart-lung interaction; neural, mechanical and humoral

Details

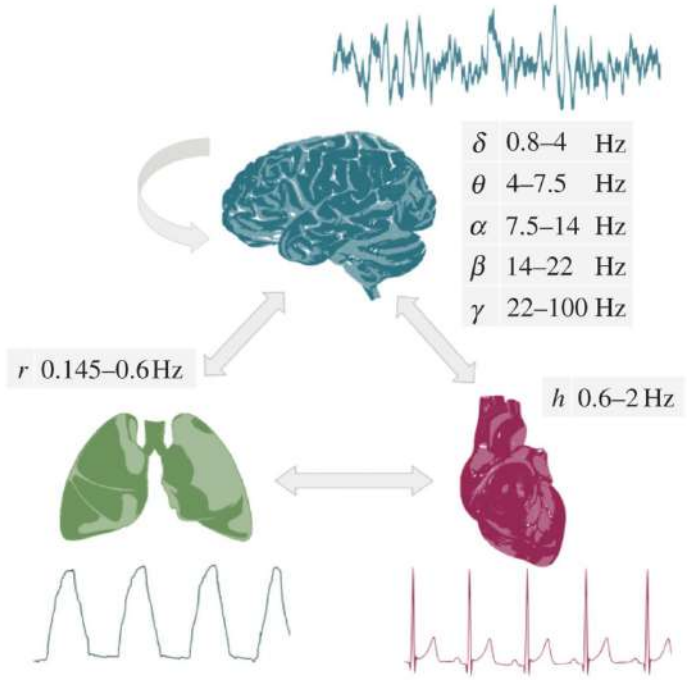
There is no measurable evidence yet for direct communication of the heart with the lungs.

BRAIN - HEART - LUNG Communication

Overview



Details

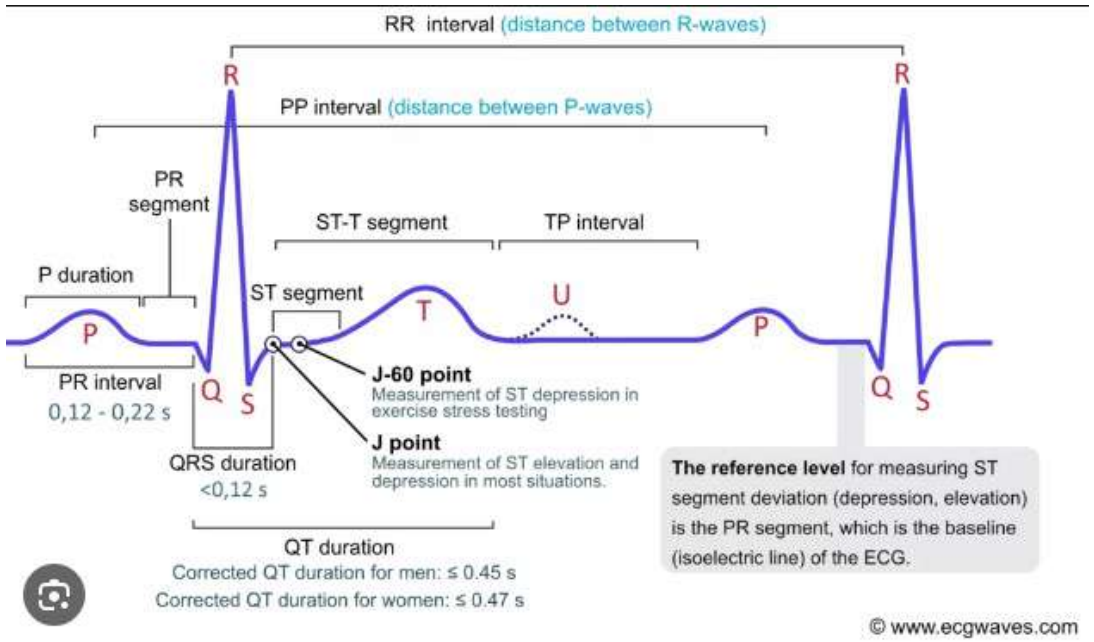


B. Electrophysiological signals in Brain, Heart, Lung

- ECG (Electrocardiogram)
- EEG (Electroencephalogram)
- Respiratory (Plethysmogram)

Information content of ECG => Heart Rate

- The ECG represents the rhythmic and synchronized function of the heart. One or up to 12 leads are used to estimate time and space of the cardiac cells re- and de-polarization.
- Classified as periodic signal (in the time domain) with narrowband spectrum (in frequency domain)



Information content of Heart Rate Signal

The heart rate variability (HRV) signal is indicative of autonomic regulation of the heart rate (HR). Classified as aperiodic signal with distinctive peaks in frequency domain

Frequency domain variables of HRV

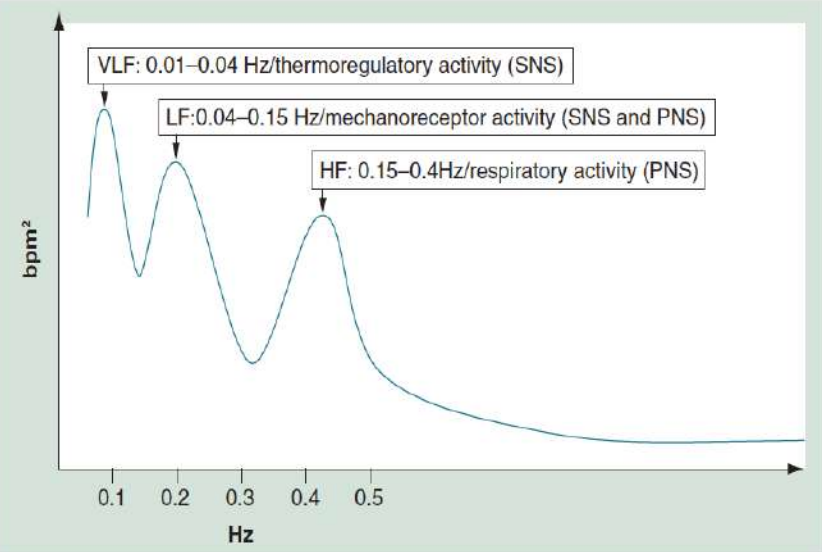
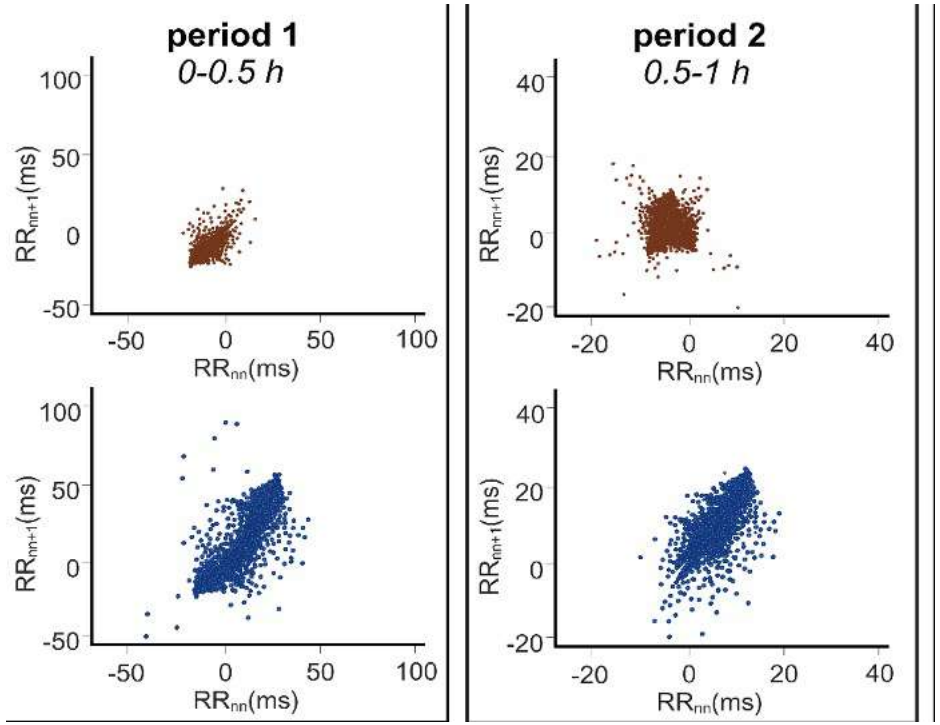


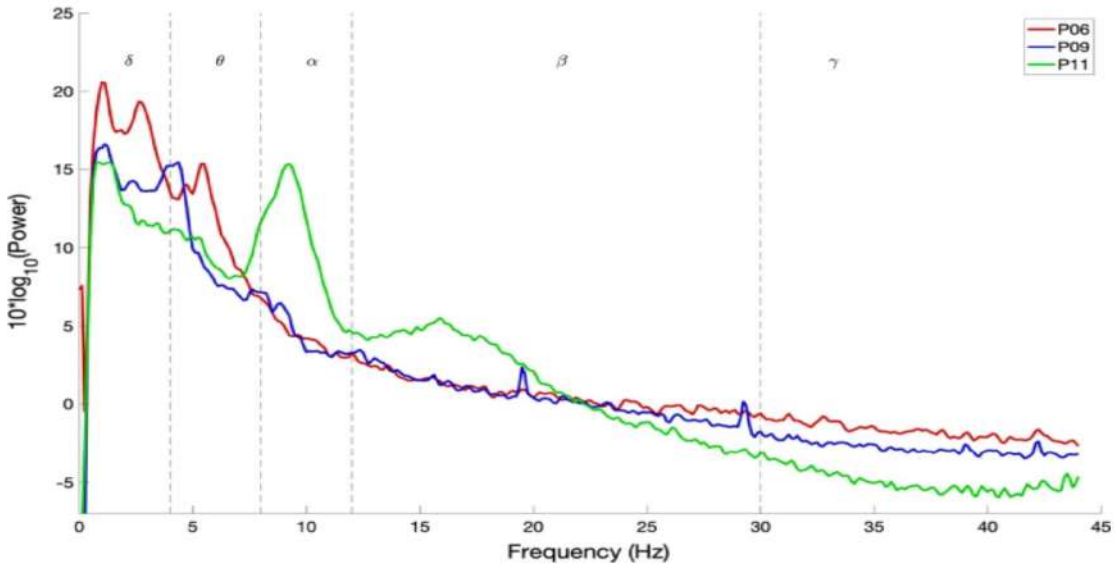
Figure 3. Heart rate variability in the frequency domain analysis.
HF: High frequency; LF: Low frequency; PNS: Parasympathetic nervous system; SNS: Sympathetic nervous system; VLF: Very-low frequency.

Poincare mapping of IBI (the inverse of HR)



Information content of EEG

- The EEG reflects synchronized neuronal activities which are associated with various cognitive and physiological processes
- EEG signals exhibit oscillatory patterns named delta (0.5-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta (13-30 Hz), and gamma (>30 Hz)
- Classified as colored noise signal (in time domain) with 1/f spectrum and distinguished peaks(in frequency domain)

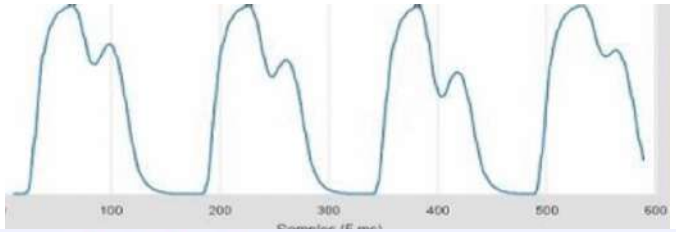


Comparison of average EEG power spectral densities in different Patients

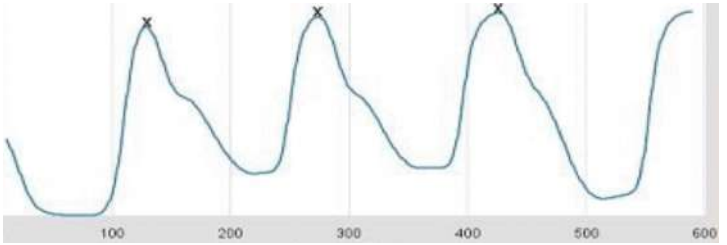
Photoplethysmography (PPG)

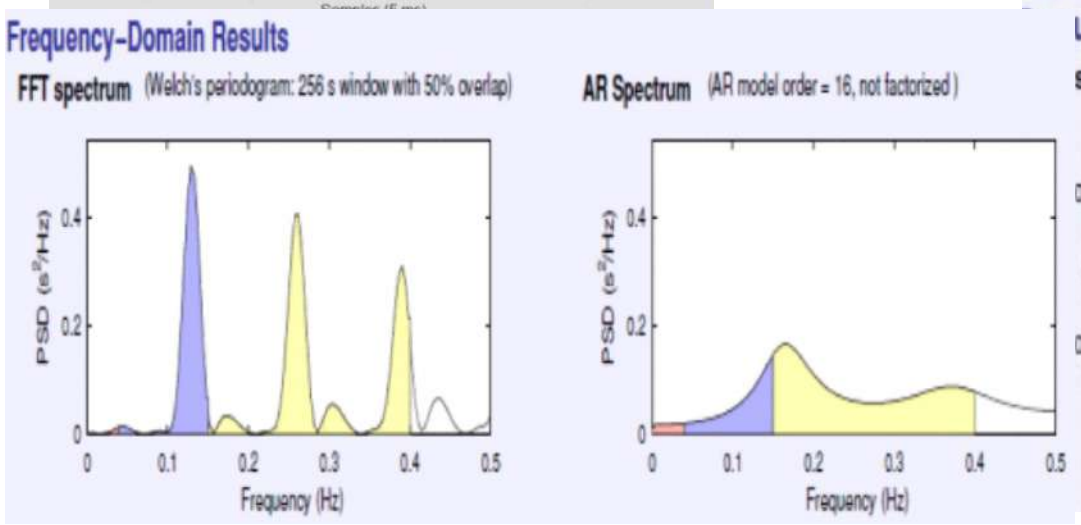
- A PPG is an optically obtained plethysmogram signal that can detect blood volume changes in tissue and extract the respiration rate among other biomarkers.

PPG in laying conditions

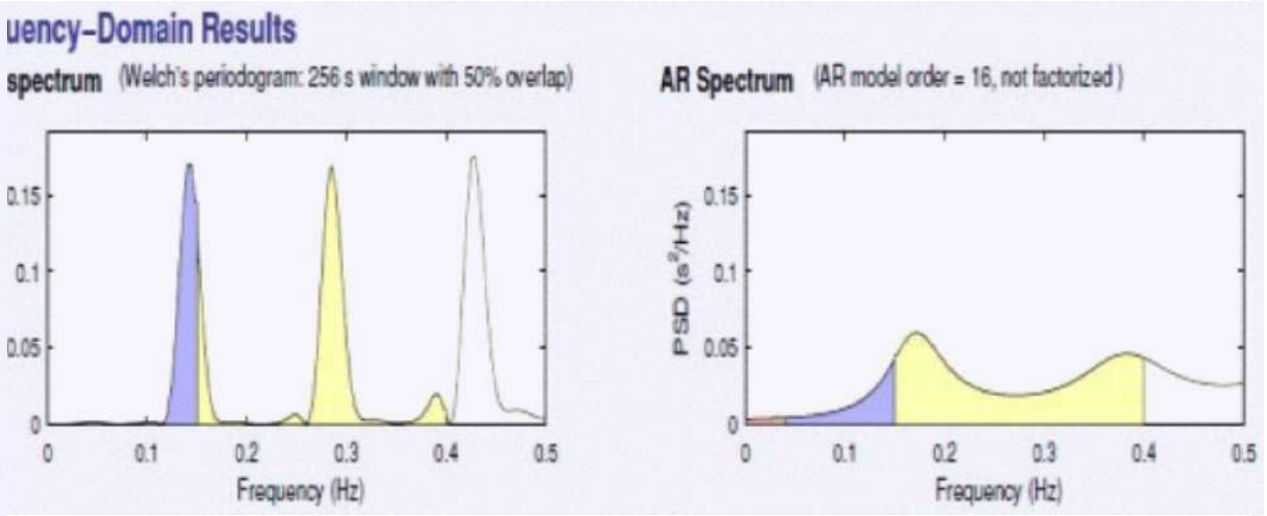


PPG in sitting conditions





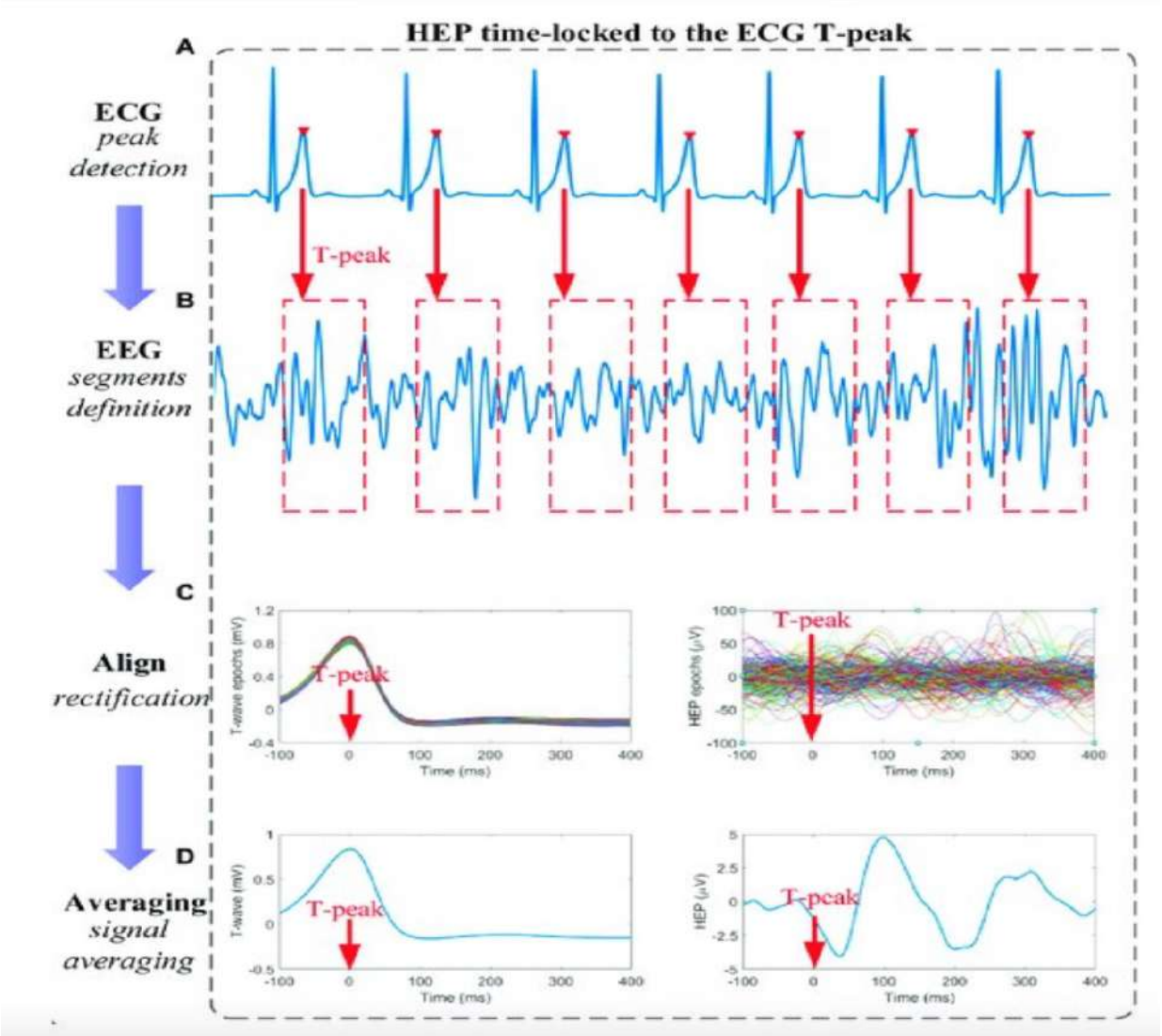
PSD by two differen methods



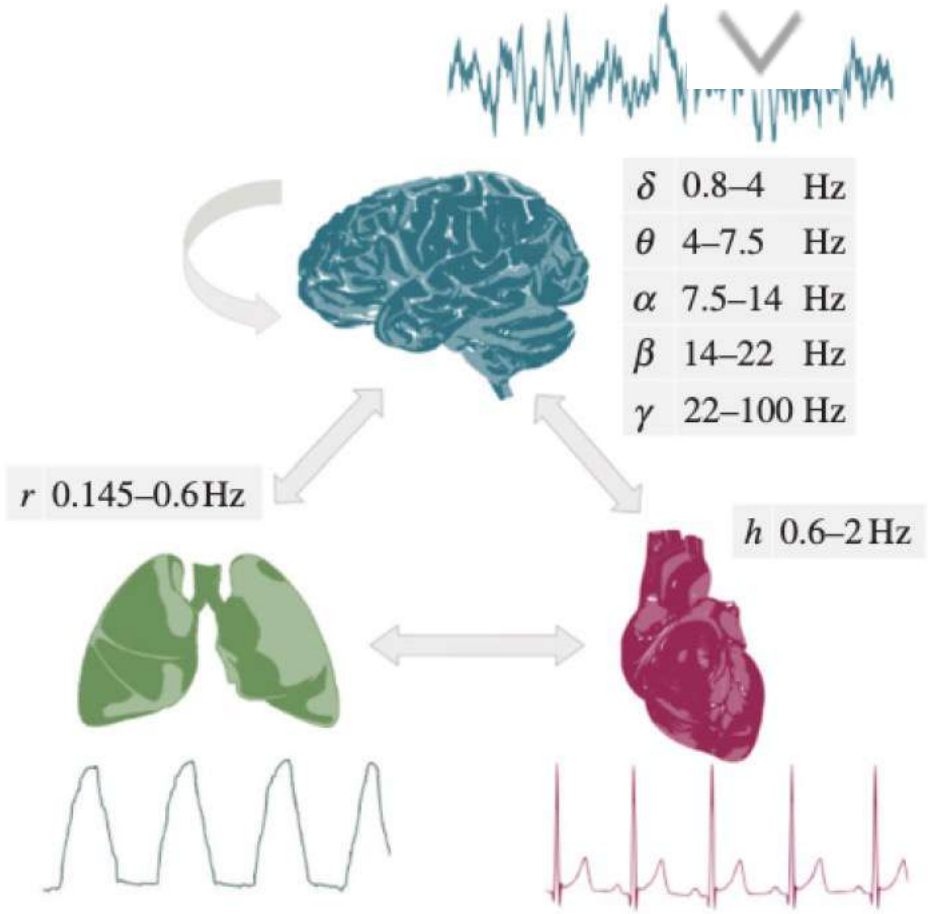
PSD by two differen methods

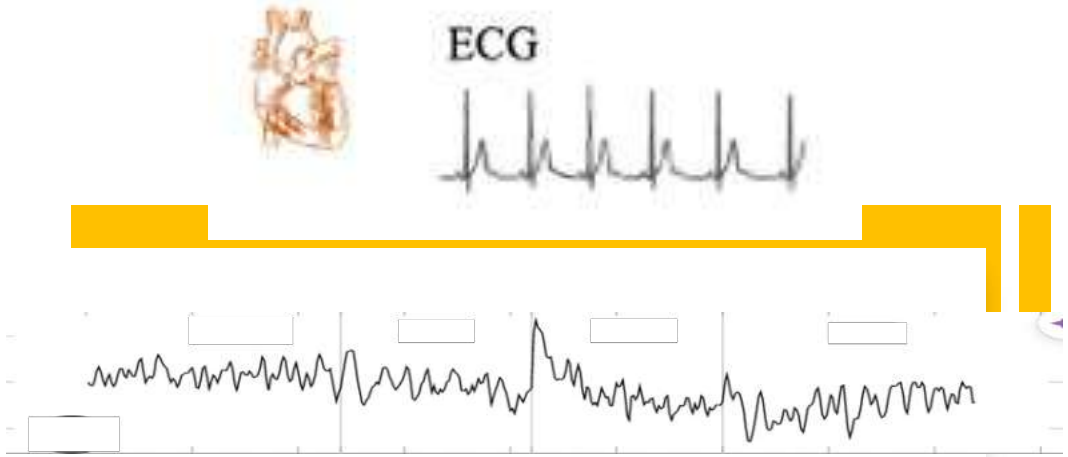
Heartbeat-evoked potentials (HEP) in the brain

- The heartbeat-evoked potentials (HEP) in the time domain: event-related potentials (ERP). And the heartbeat-evoked oscillations (HEO) in the time-frequency domain: This approach examines how the brain processes each heartbeat and captures brain activity that affects the timing and intensity of subsequent heartbeats. (bidirectional interaction) With millisecond (ms) accuracy, this method requires that both time series are perfectly synchronized and that the heartbeats are marked in the EEG signals.
- Applications in; Somatosensory Perception, Interoceptive-Exteroceptive Integration-Meditation, Cognition

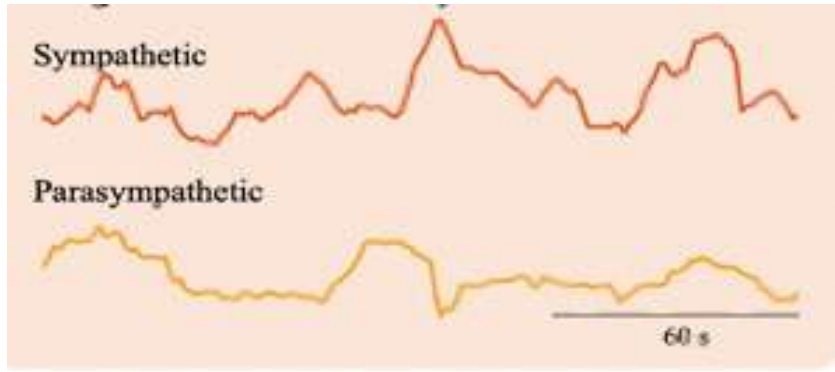


Cortical, Heart and Lung Signals





RR tme series)



Time series of the the two components of RR signal

C. BrainBeats software

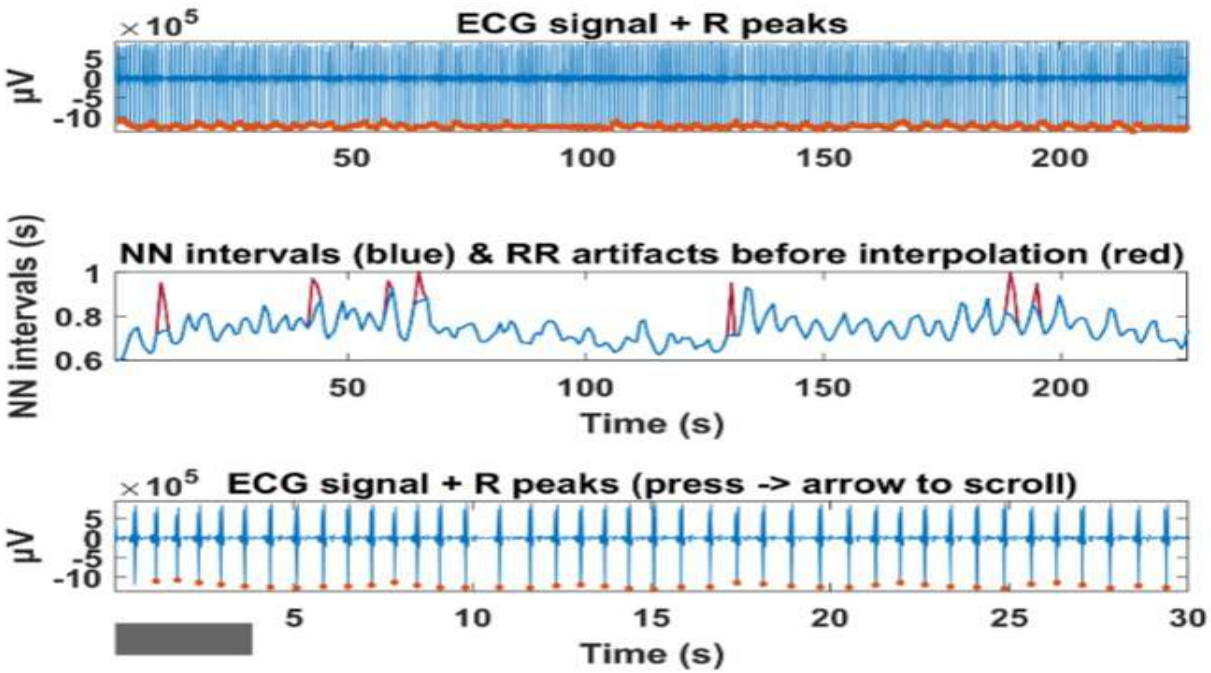
BrainBeats, an Open-Source EEGLAB Plugin to Jointly Analyze EEG and Cardiovascular Signals

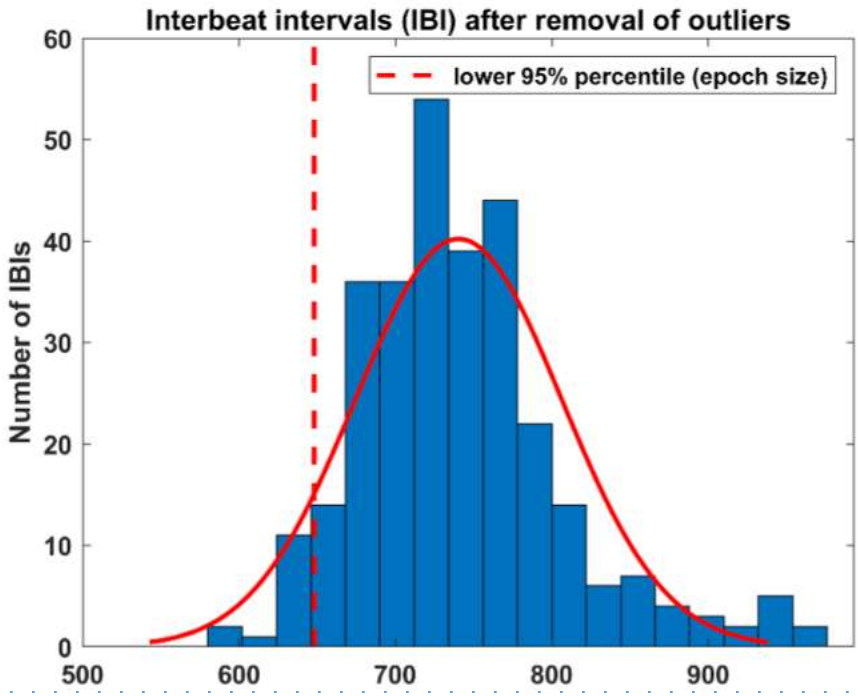
Published: April 26, 2024 doi: 10.3791/65829

- The purpose of the BrainBeats toolbox is to develop algorithms for analyzing brain and body signals, specifically EEG, PPG, and ECG signals. It offers three main protocols;
- heartbeat-evoked potentials (HEP) and oscillations (HEO),
- feature-based analysis, and
- heart artifact extraction from EEG signals.

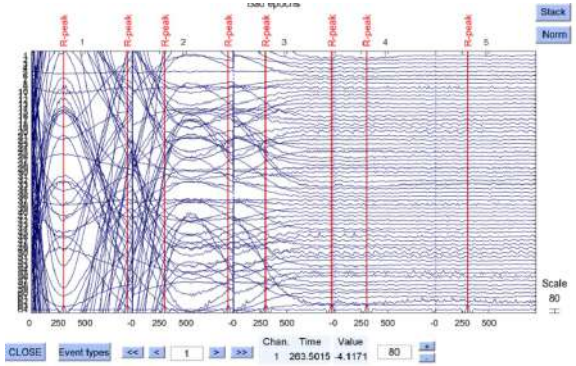
Indicative Results_1

RR intervals, artifacts, and NN intervals obtained from ECG signal.

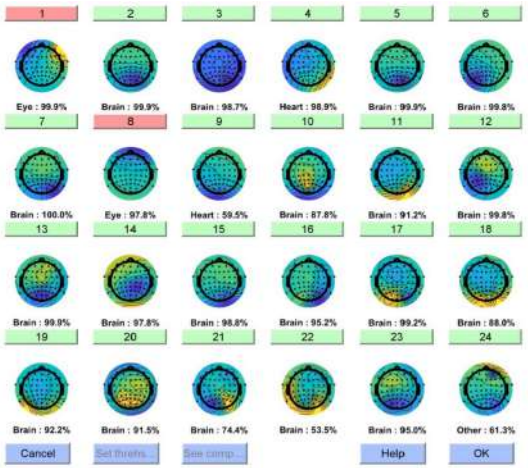




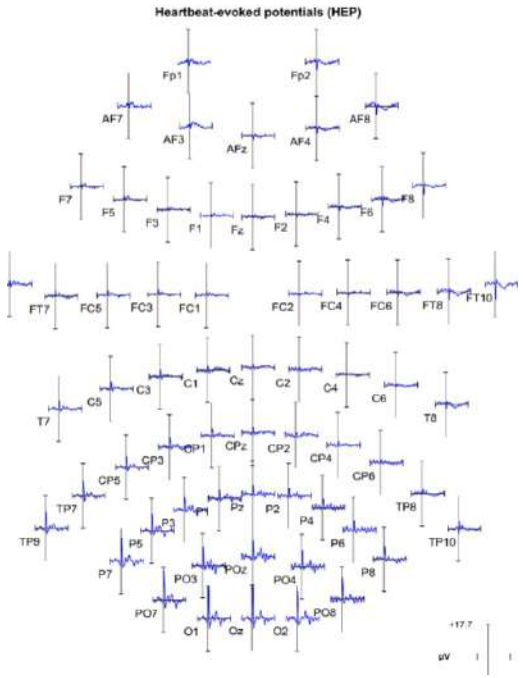
Indicative Results_2
EEG processing and features extractions.



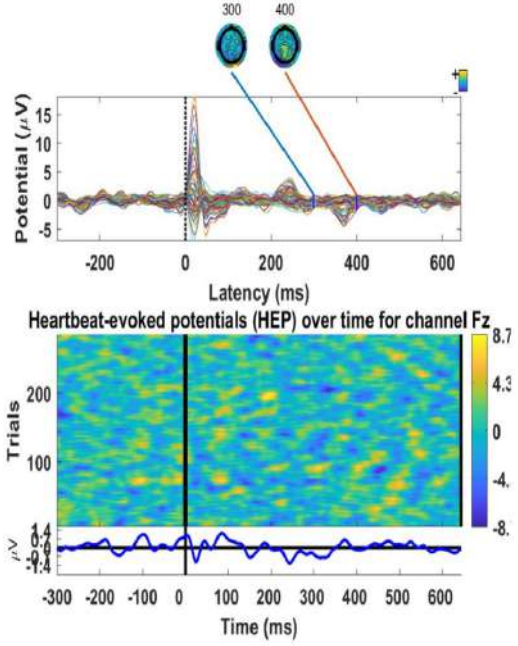
Removal of artifactual epochs.



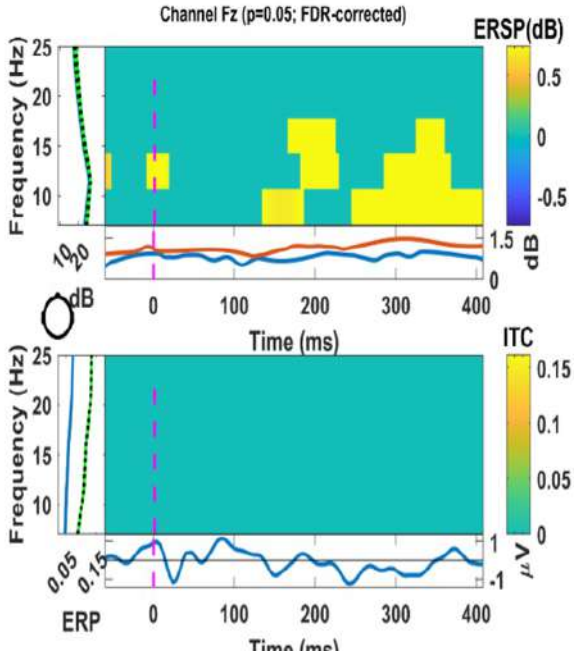
Classification of the independent components to remove non-brain artifacts



Visualization of the heartbeat-evoked potentials (HEP) for each EEG channel obtained from the ECG signal.

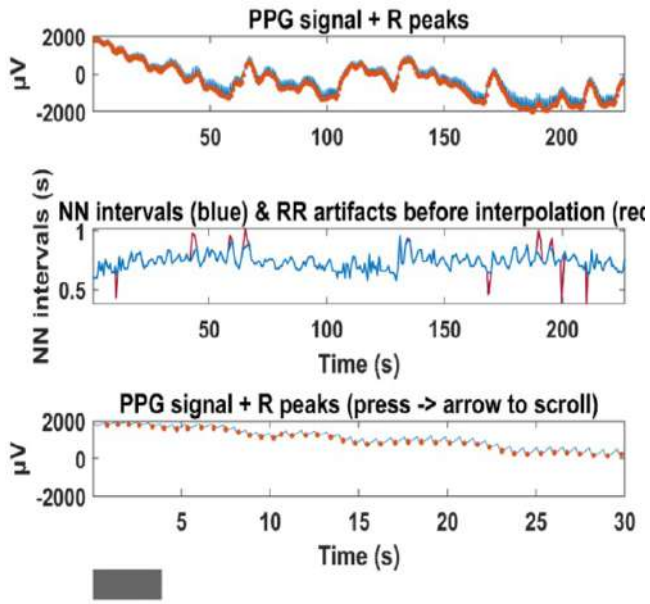


Grand average heartbeat-evoked potentials (HEP) obtained with ECG (time domain)

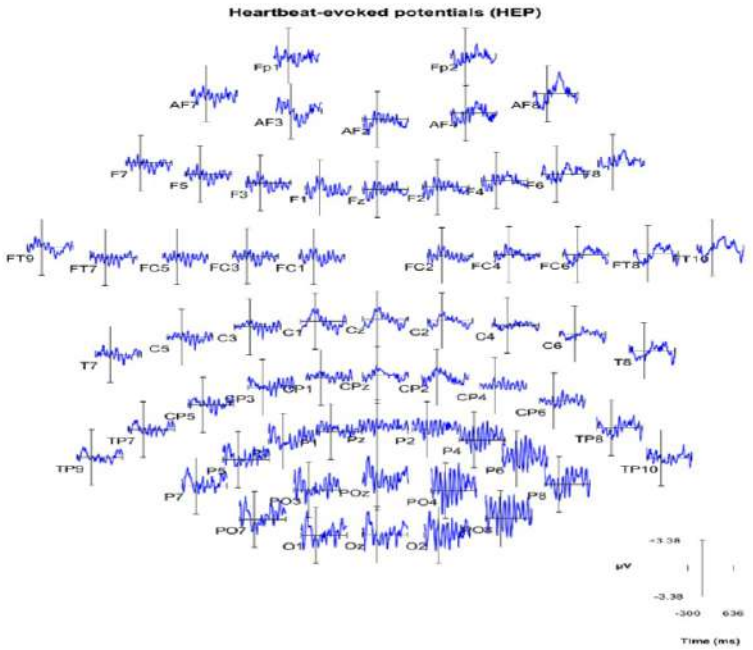


Heartbeat-evoked oscillations (HEO) obtained from ECG (frequency domain).

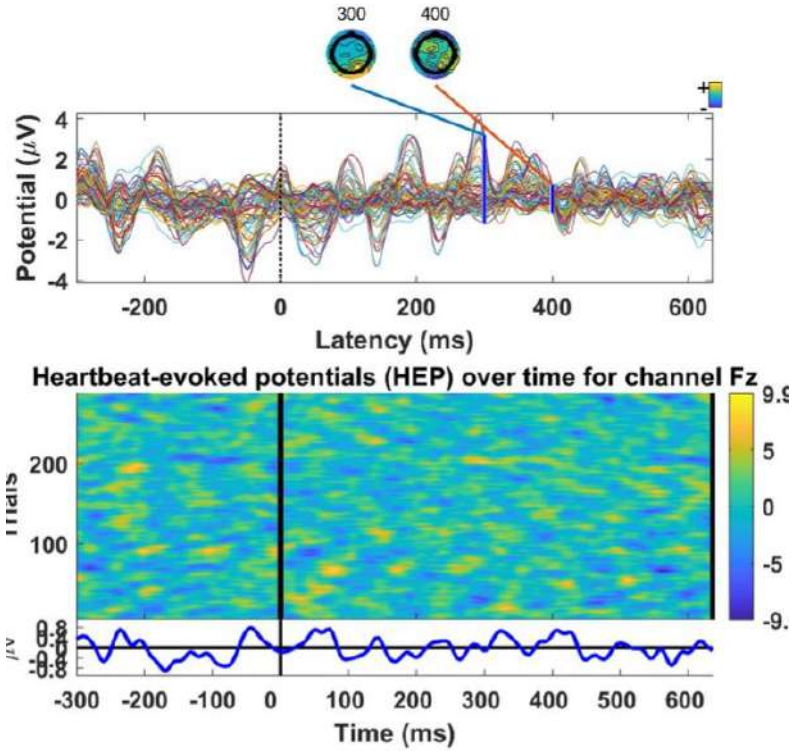
Indicative Results_3
RR intervals, artifacts, and NN intervals obtained from PPG signal.



Step by step analysis of PPG signal

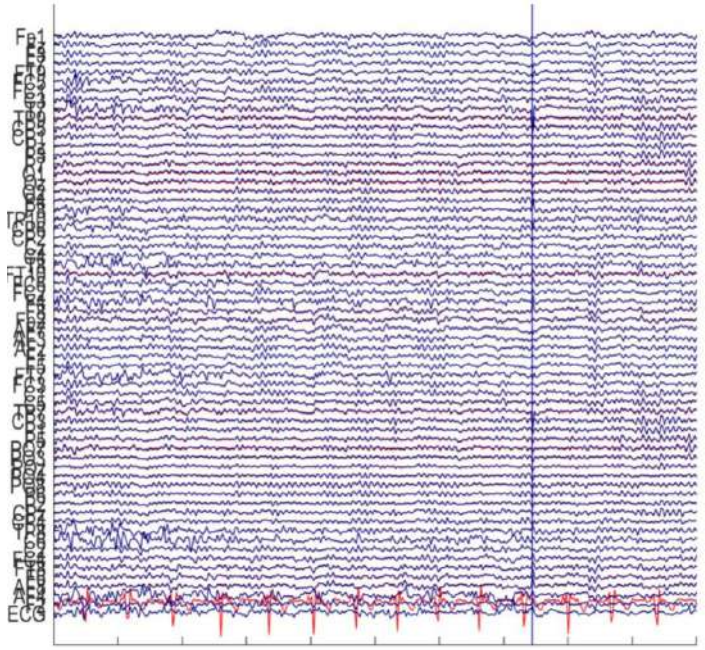


Visualization of the heartbeat-evoked potentials (HEP) obtained from the PPG signal for each EEG channel

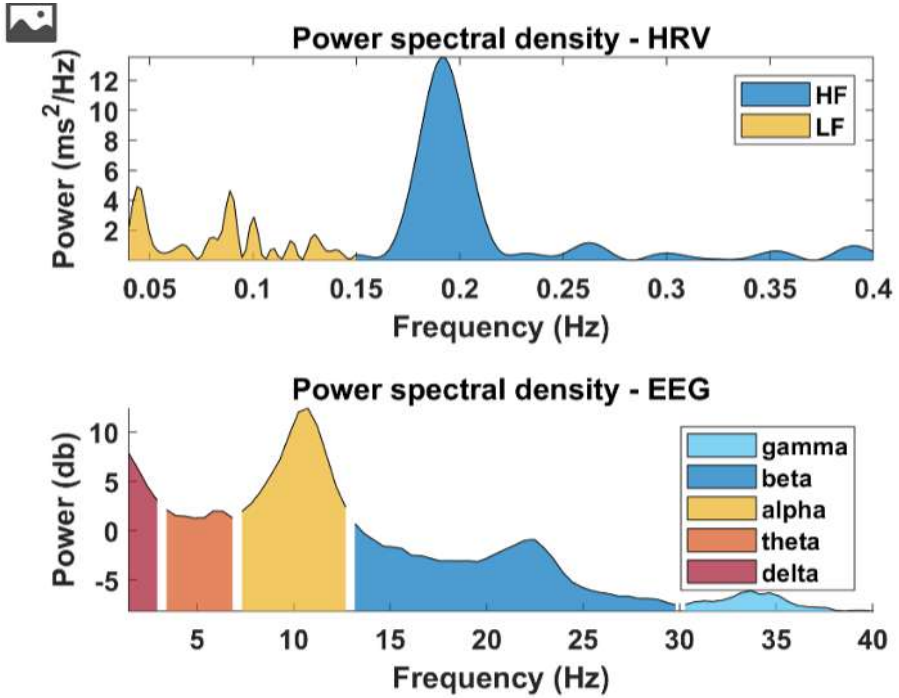


Grand average heartbeat-evoked potentials (HEP) obtained with PPG

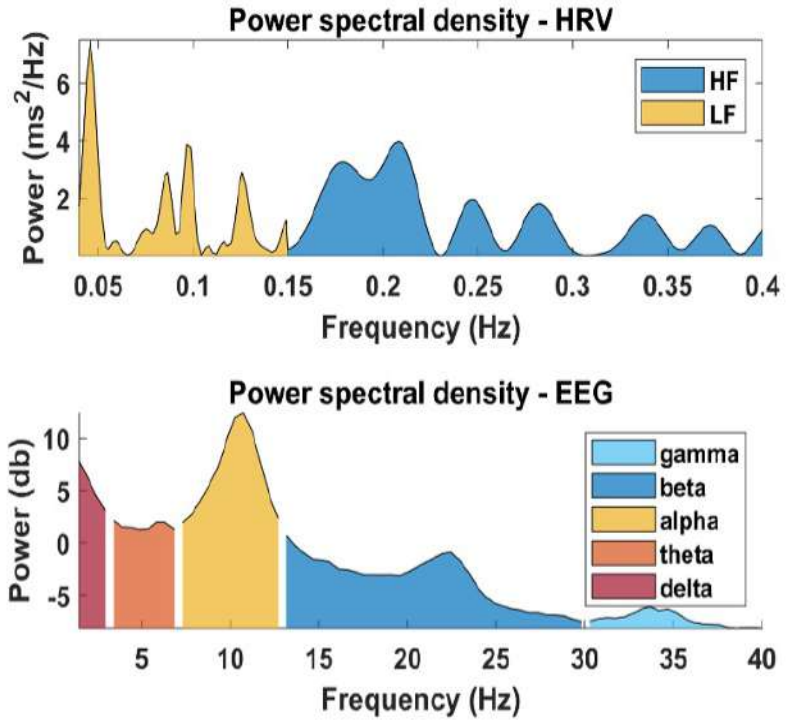
Indicative Results_4
EEG signal analysis



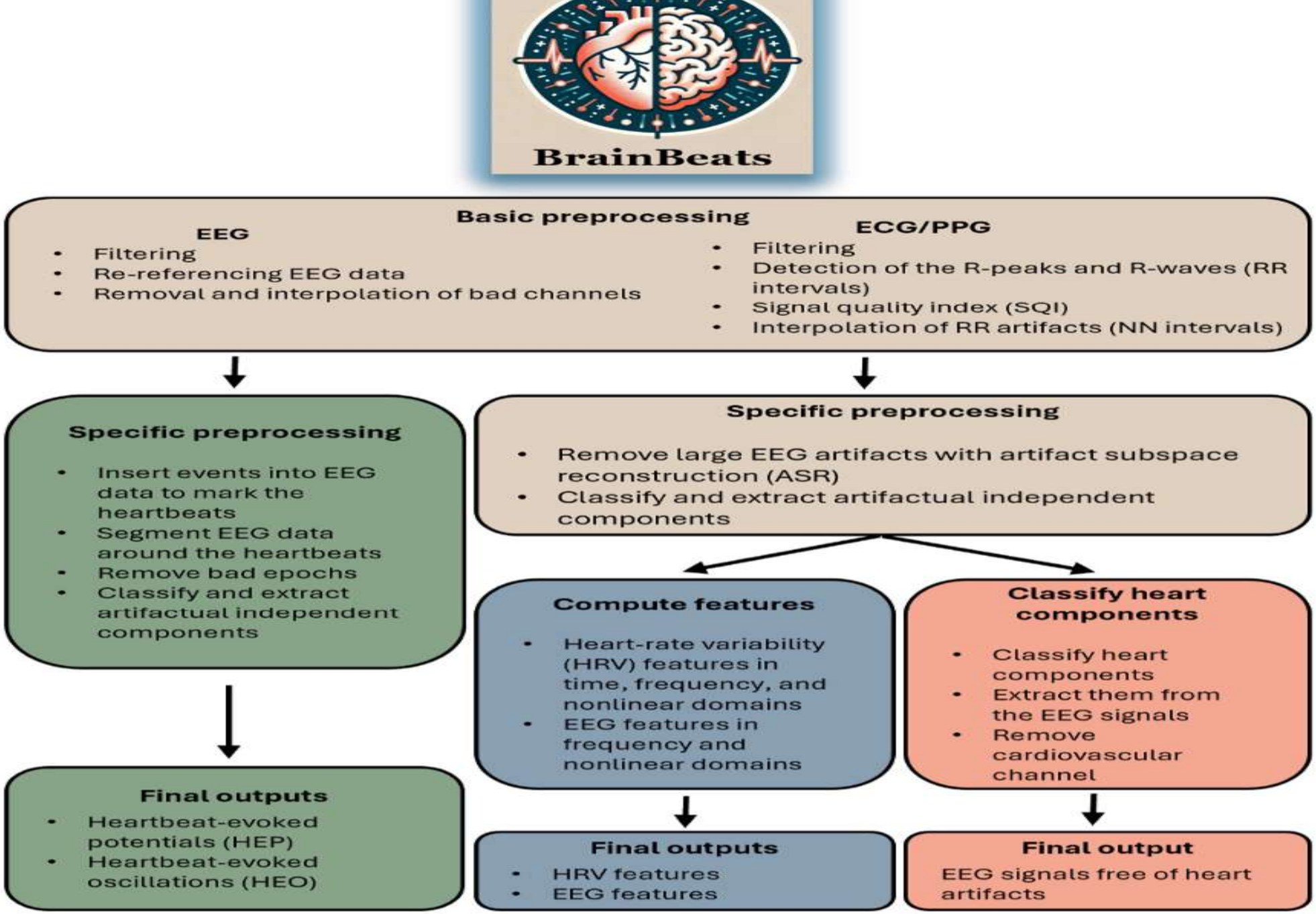
Visualization of EEG channels (in blue) after extracting heart artifacts (in red)



PSD extracted from RR intervals (ECG) and EEG signals



PSD extracted from RR intervals (PPG) and EEG signals



Block diagram summarizing BrainBeats' overall architecture and flow.

Novelties brought by BrainBeats relative to pre-existing, similar methods

METHOD	Detect R-peaks from ECG	Detect R-waves from PPG	HEP/HEO	EEG & HRV features	Remove heart artifacts from EEG	GUI	Command line
ecg-kit	X	X	X				X
BeMoBIL	X		X				X
HEPLAB	X		X			X	X
CARE-rCortex	X		X			X	X
BrainBeats	X	X	X	X	X	X	X

D. Brain - Heart - Lung experimental data analysis using GPDC

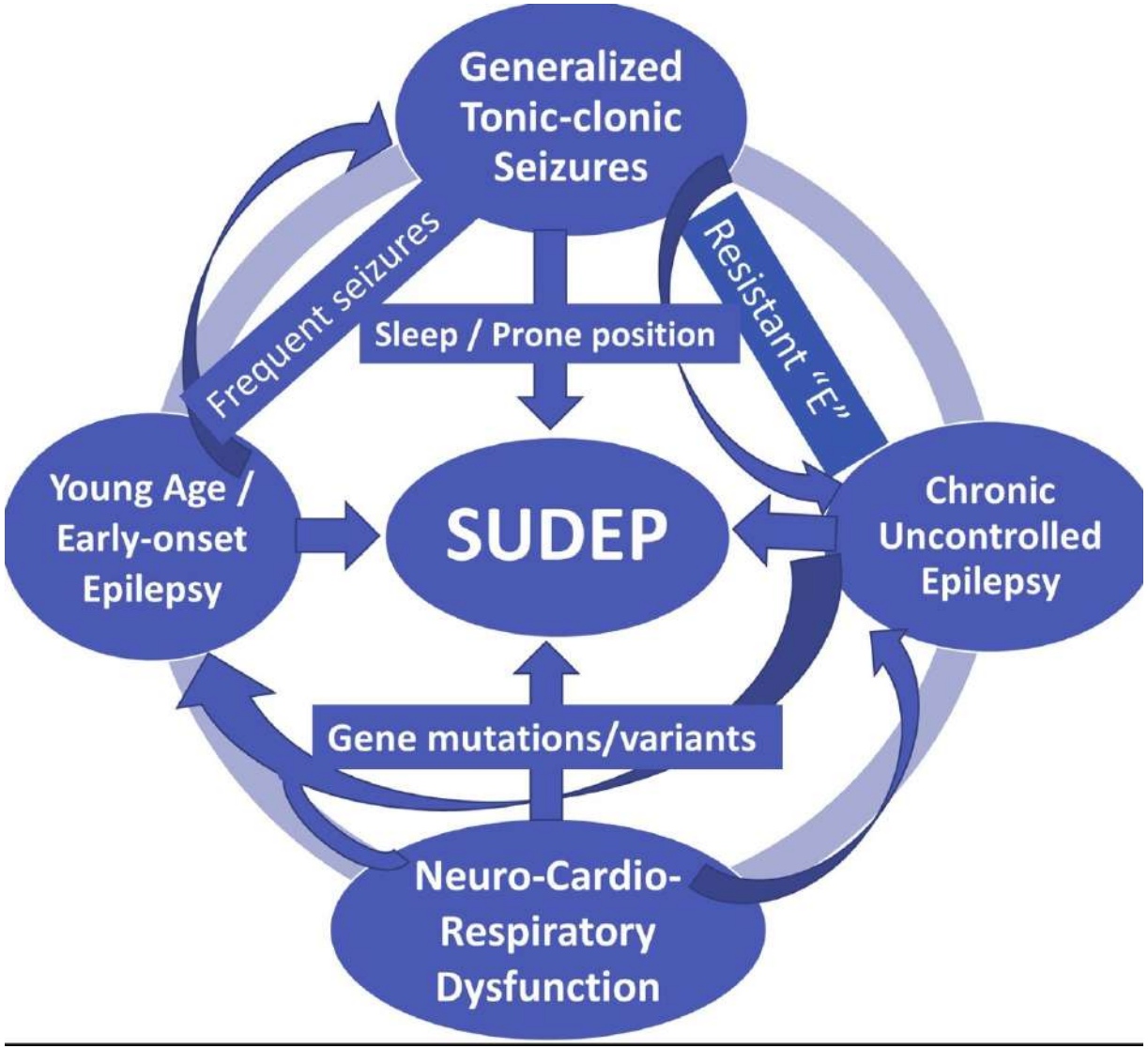
What is Epilepsy?

Epilepsy is a chronic neurological disorder characterized by a predisposition of the brain to recurrent seizures. Seizures result from abnormally endured synchronization of brain sites and are characterized by pathologically high electrical activity that propagates from the epileptogenic focus and interferes with normal brain sites. The prevalence of epilepsy is significant, affecting approximately 1% of the general population. Approximately 1/3 of the patients with epilepsy experience seizures that are not controlled by anti-seizure medication.

An example of an electroencephalogram (EEG) signature of a focal seizure that propagates from the epileptogenic focus to other brain sites within seconds.

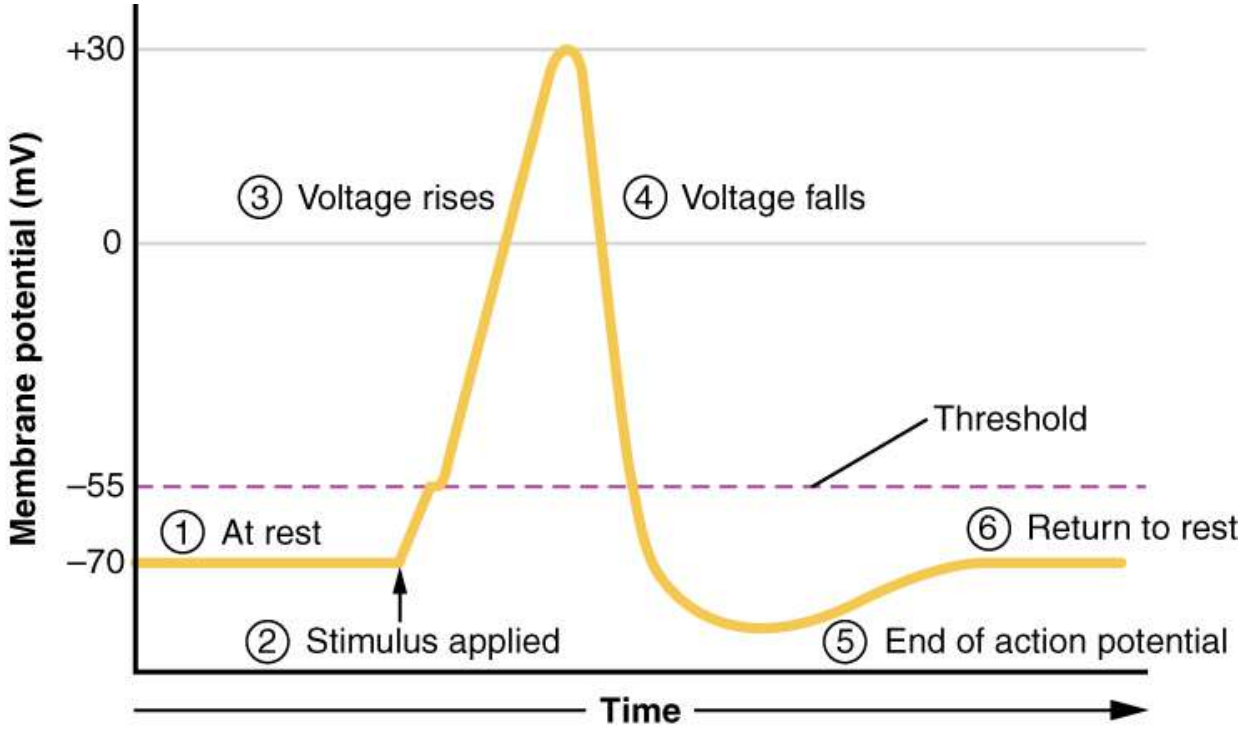
What is SUDEP?

Sudden, Unexpected Death in Epilepsy (SUDEP) is the sudden, unexpected death of someone with epilepsy. In SUDEP cases, no apparent cause of death is found when an autopsy is done. Each year, more than 1 in 1,000 people with epilepsy die from SUDEP. This is the leading cause of death in people with uncontrolled seizures



The SUDEP Susceptibility Model: Kcna1 knockout (KO)

- A genetic model of SUDEP susceptibility
- Exhibits loss of function in the voltage-gated Kv1.1 potassium channel α-subunits.
- This causes a state of constant excitation in the brain by reducing the hyperpolarization of neurons following the initial excitation (depolarization).
- Kcna1-knockout mice are constantly excited and SUDEP-prone.



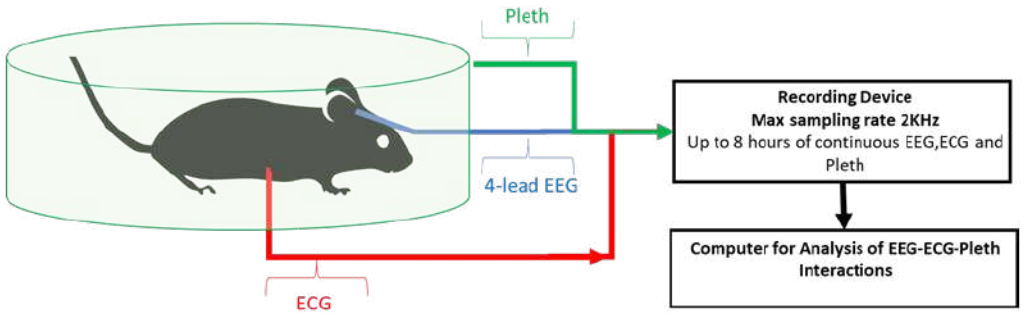
Example of action potential

(https://commons.wikimedia.org/wiki/File:1222_Action_Potential_Labels.jpg)

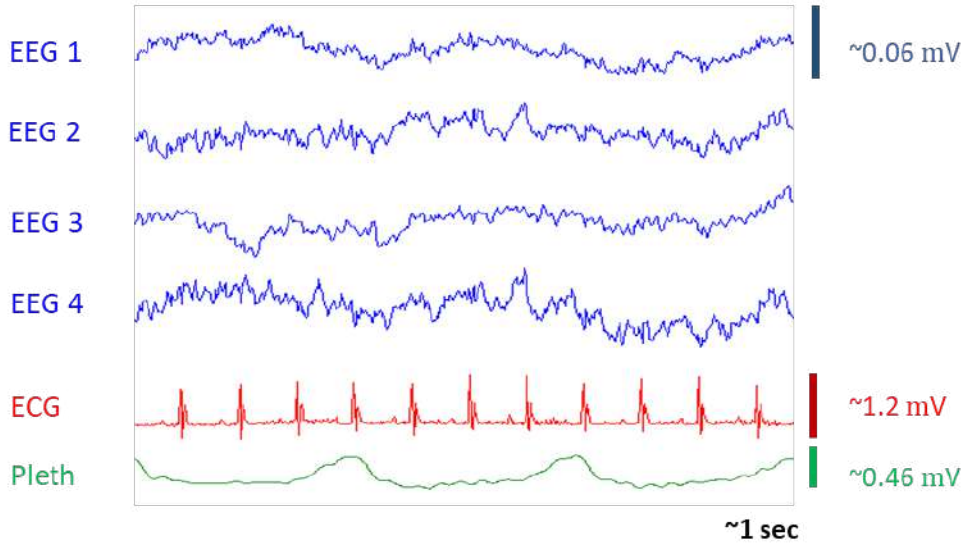
Data Collection

- The animals (7 WT and 8 KO) are placed in an Unrestrained Whole Body Plethysmography (UWBP) chamber to record Pleth data.
- EEG-ECG-Pleth Signals are recorded continuously for 8 hours
- Both EEG and ECG are sampled at 1 kHz and Pleth is sampled at 500 Hz.
- EEG and ECG are downsampled to match Pleth sample rate (500 Hz)

(a)



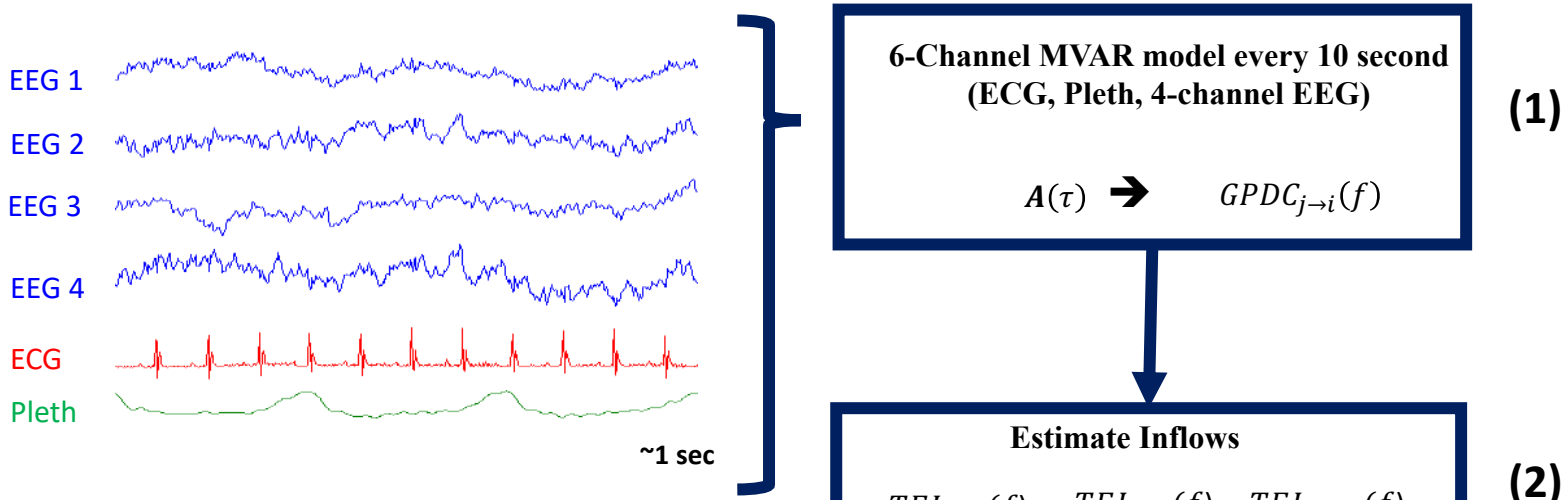
(b)



Barrow Neurological Institute

Hutson et al., "Directed Connectivity Analysis of the Neuro-Cardio- and Respiratory Systems Reveals Novel Biomarkers of Susceptibility to SUDEP," in IEEE Open Journal of Engineering in Medicine and Biology, vol. 1, pp. 301-311, 2020, doi:

Data Analysis



Flow chart for EEG-ECG-Pleth data analysis.

Hutson et al., "Directed Connectivity Analysis of the Neuro-Cardio- and Respiratory Systems Reveals Novel Biomarkers of Susceptibility to SUDEP," in IEEE Open Journal of Engineering in Medicine and Biology, vol. 1, pp. 301-311, 2020, doi:

Generalized Partial Directed Coherence

Epileptogenic Focus Localization from iEEG or Source Space Converted MEG

- Interictal data are segmented into non-overlapping 10sec windows
- A Multi-Variate AutoRegressive (MVAR) model is estimated per window:

$$X(t) = \sum_{\tau=1}^{p} \boldsymbol{A}(\tau) X(t-\tau) + E(t)$$

where (p) is the model order, and (τ) is the time delay in data points.

- Taking the discrete Fourier Transform:

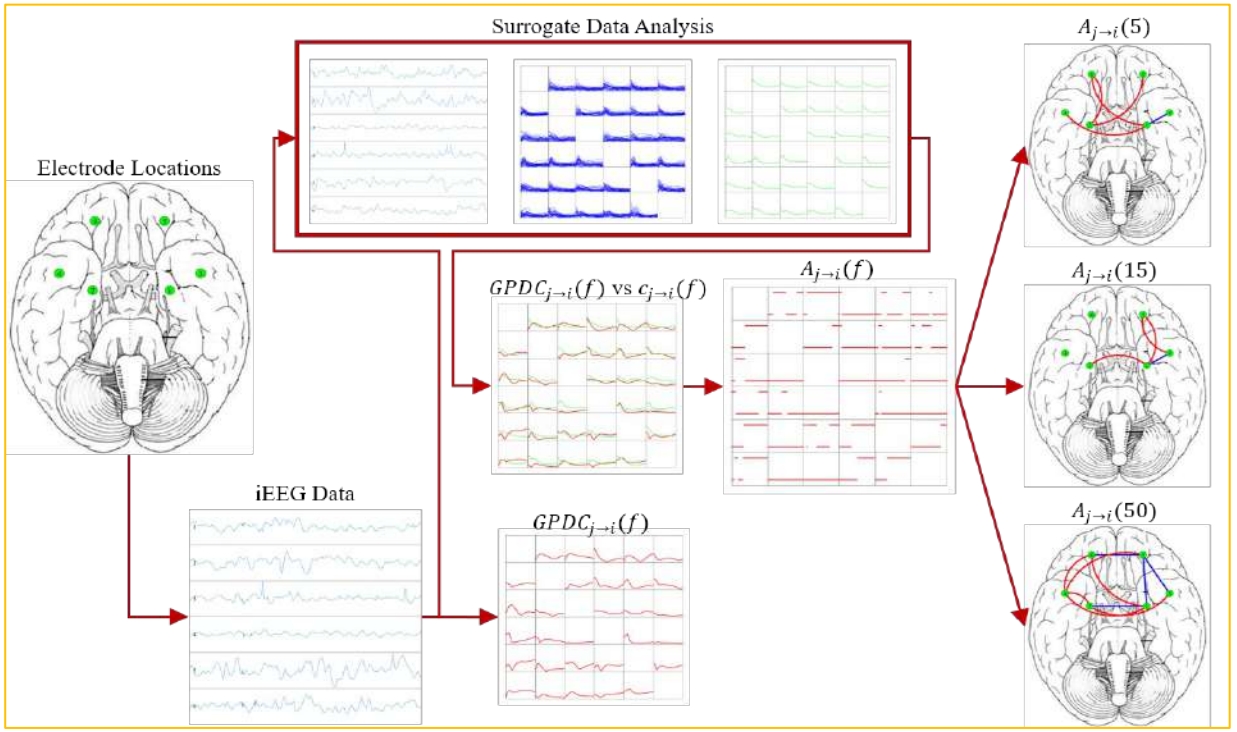
$$\boldsymbol{B}(f) = I - \sum_{\tau=1}^{p} \boldsymbol{A}(\tau) e^{-i2\pi f \tau}$$

- After using spectral factorization theorem on the $\boldsymbol{B}(f)$, GPDC is defined as:

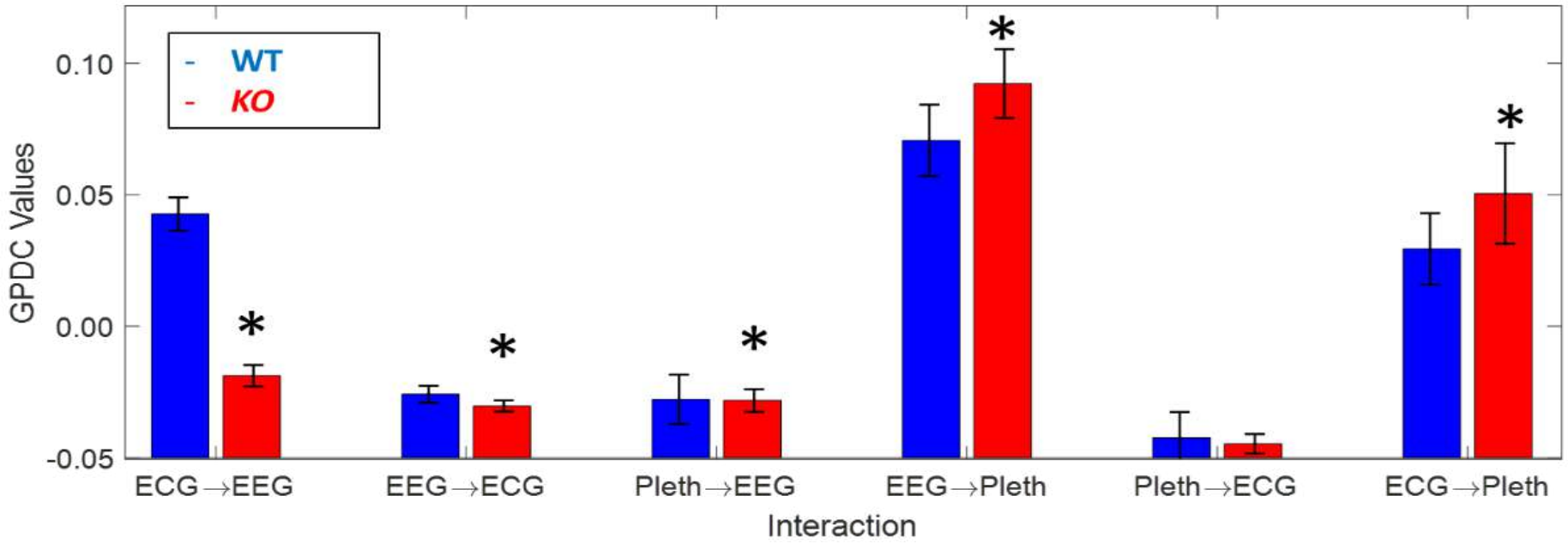
$$GPDC_{j\to i}(f) = \frac{\left|\boldsymbol{B}_{ij}(f)\right|}{\sqrt{\sum_{k=1}^{N} \frac{\left|\boldsymbol{B}_{kj}(f)\right|^2}{\sigma_{kk}^2}}}$$

where σ_{ii} are obtained from the covariance matrix $\boldsymbol{S} = \left[\sigma_{ij}\right]_{i,j=1,\ldots,N}$ of the noise process $E(t)$, $\boldsymbol{B}_{ij}(f)$ is the $(i,j)^{th}$ element of the matrix $\boldsymbol{B}(f)$.

- Sites with Maximal Inflow are determined for every 10s window, and the percentage of time each site with maximum inflow within the considered interictal period is registere.

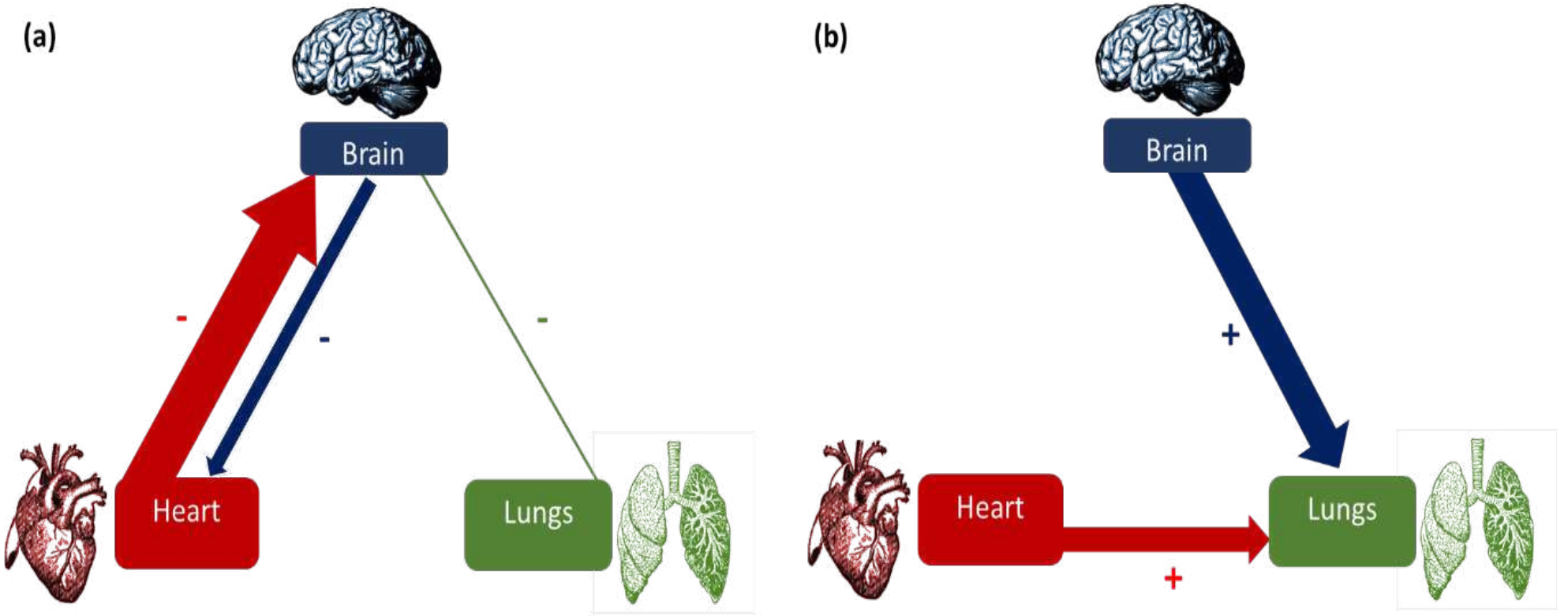


Robust Connectivity Across Frequencies: *Comparing Genotypes*



Hutson et al., "Directed Connectivity Analysis of the Neuro-Cardio- and Respiratory Systems Reveals Novel Biomarkers of Susceptibility to SUDEP," in IEEE Open Journal of Engineering in Medicine and Biology, vol. 1, pp. 301-311, 2020, doi:

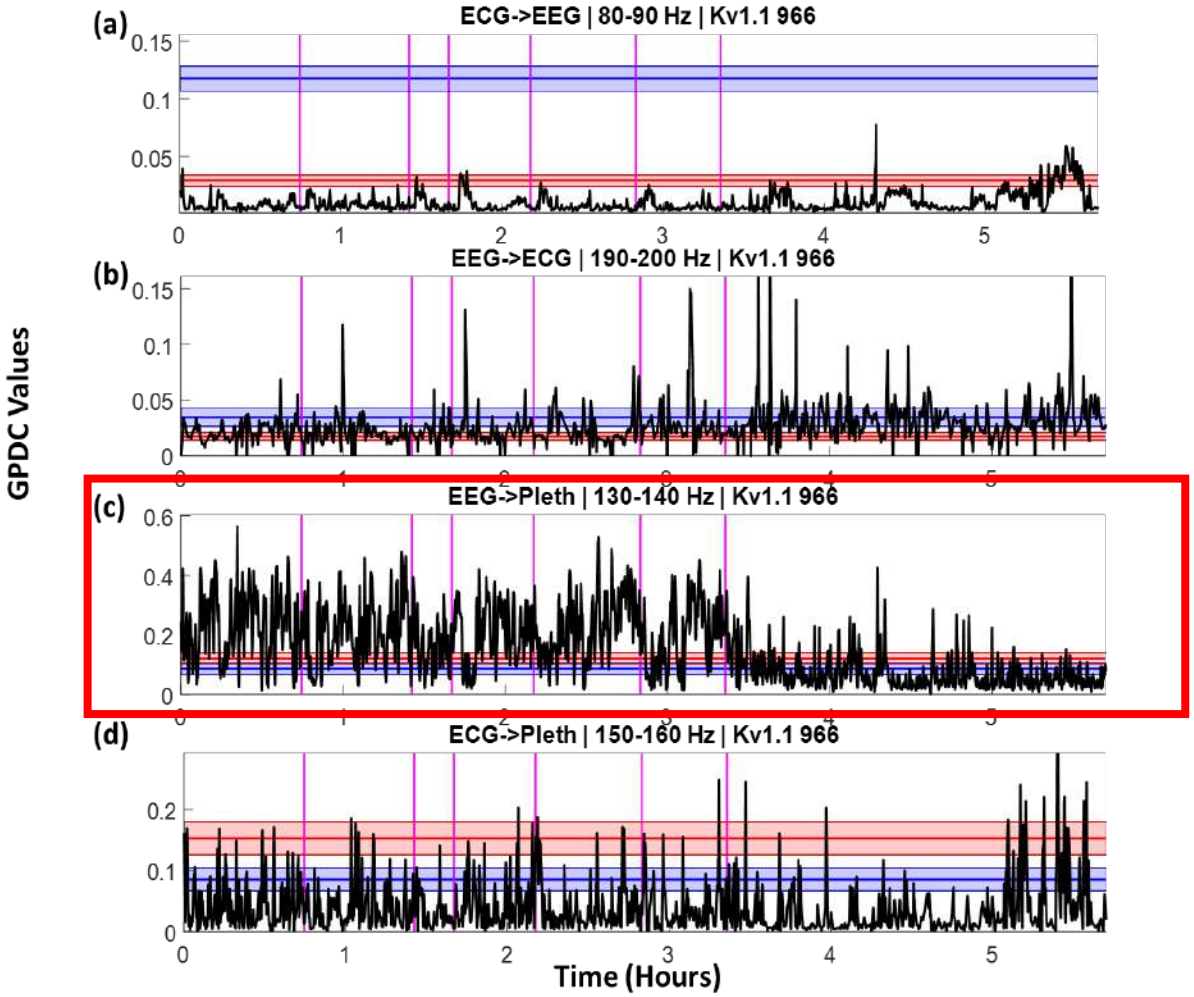
Schematic Representation: *Comparing Genotypes*



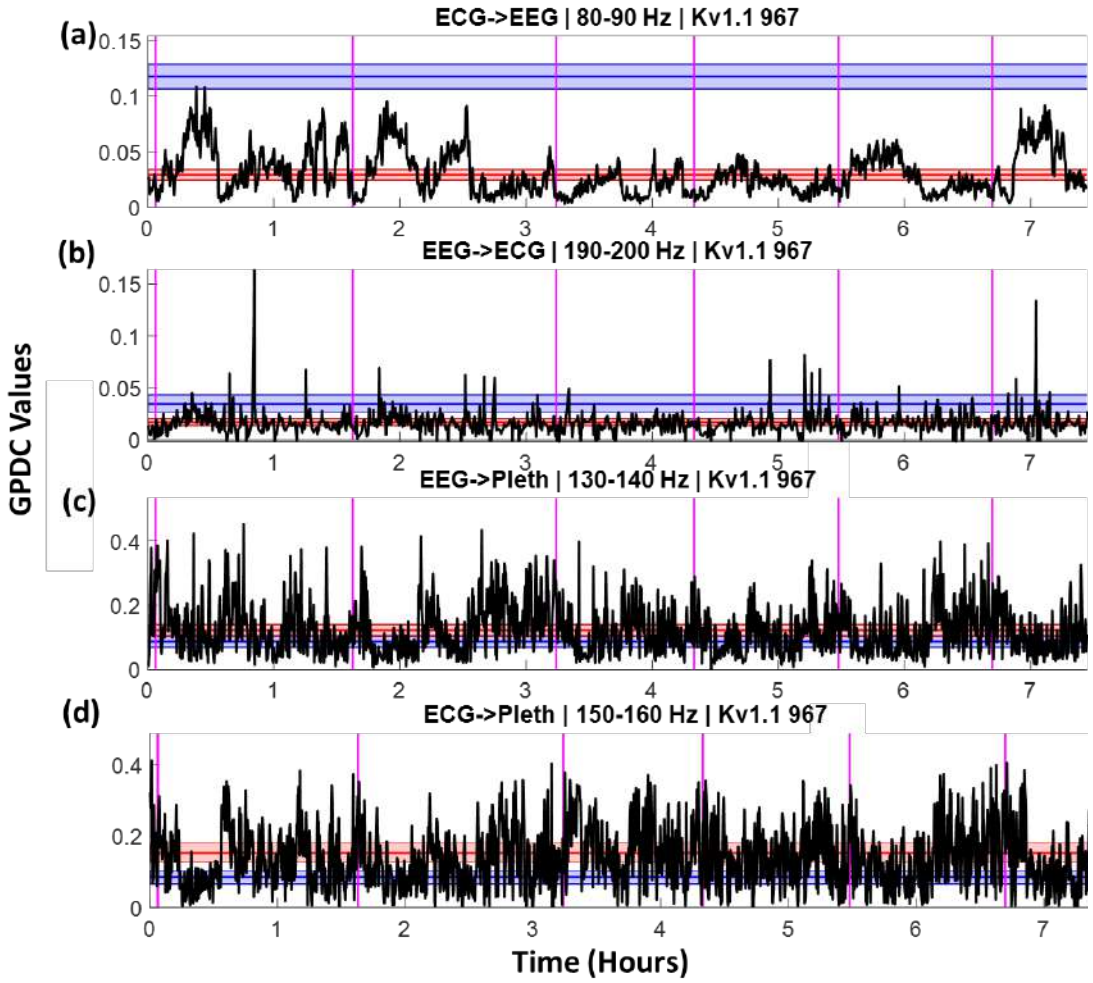
Hutson et al., "Directed Connectivity Analysis of the Neuro-Cardio- and Respiratory Systems Reveals Novel Biomarkers of Susceptibility to SUDEP," in IEEE Open Journal of Engineering in Medicine and Biology, vol. 1, pp. 301-311, 2020, doi:

Ictal Connectivity Dynamics

Animal 1



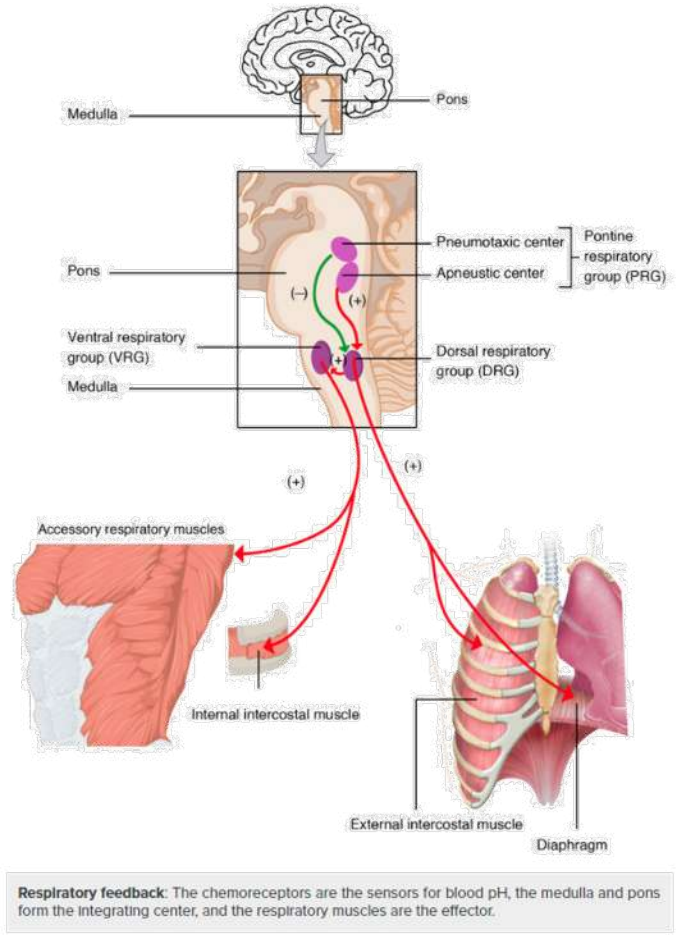
Animal 2



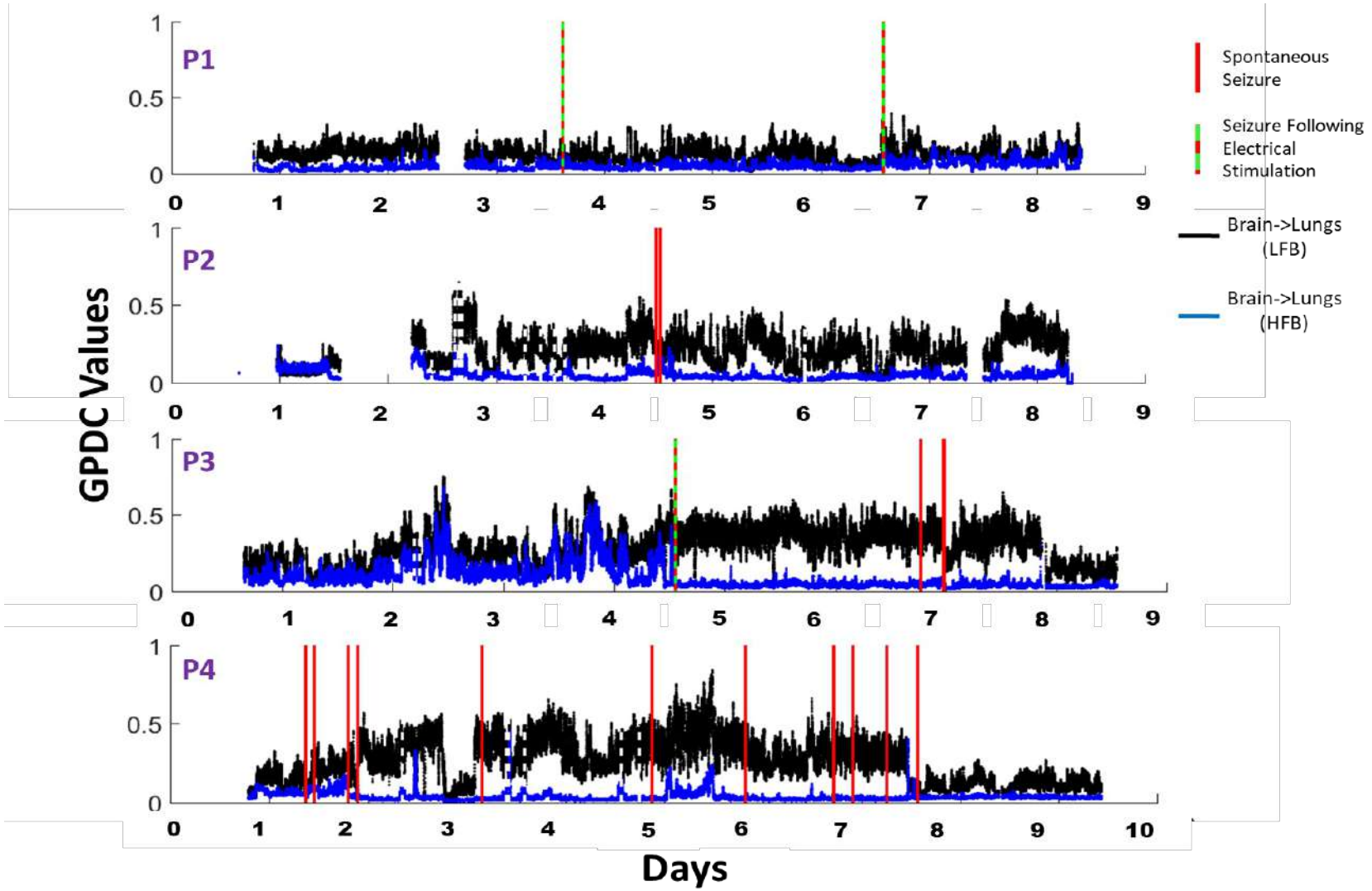
Barrow Neurological Institute

Hutson et al., "Directed Connectivity Analysis of the Neuro-Cardio- and Respiratory Systems Reveals Novel Biomarkers of Susceptibility to SUDEP," in IEEE Open Journal of Engineering in Medicine and Biology, vol. 1, pp. 301-311, 2020, doi:

Ictal Connectivity Dynamics: *Human Subjec*



SOURCE: https://courses.lumenlearning.com/boundless-ap/chapter/respiration-control/

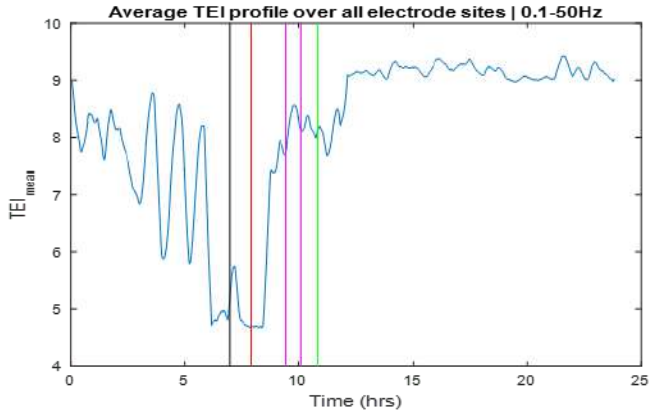


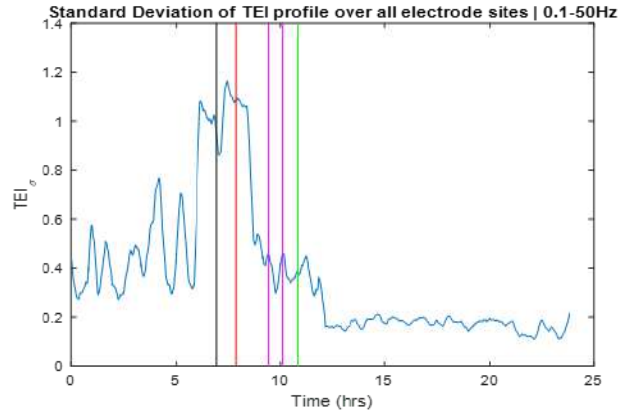
Hutson et al., "Neuro-Respiratory Connectivity During Periods of Susceptibility to Seizures", American Epilepsy Society Annual Meeting, Chicago IL, 2021

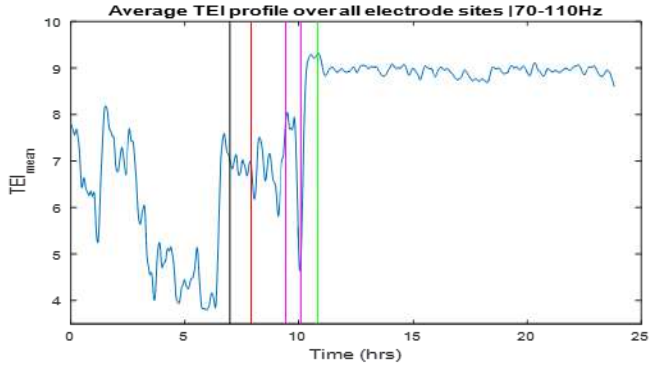
Barrow Neurological Institute

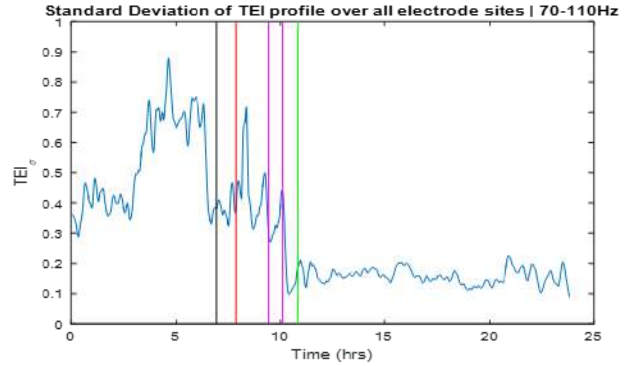
Brain Connectivity through Status Epilepticus

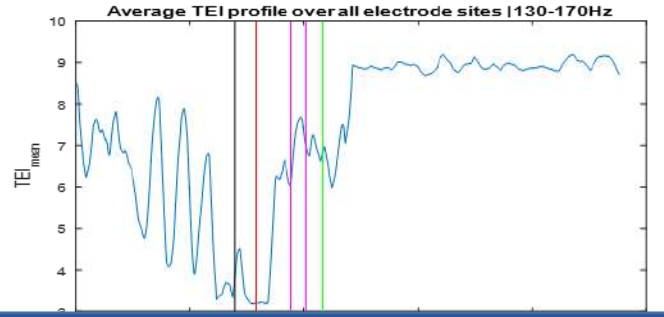
Global Brain Connectivity

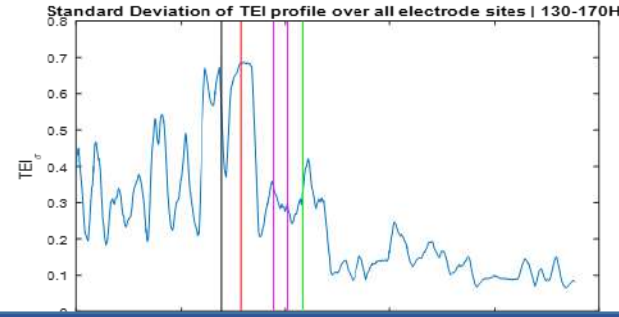












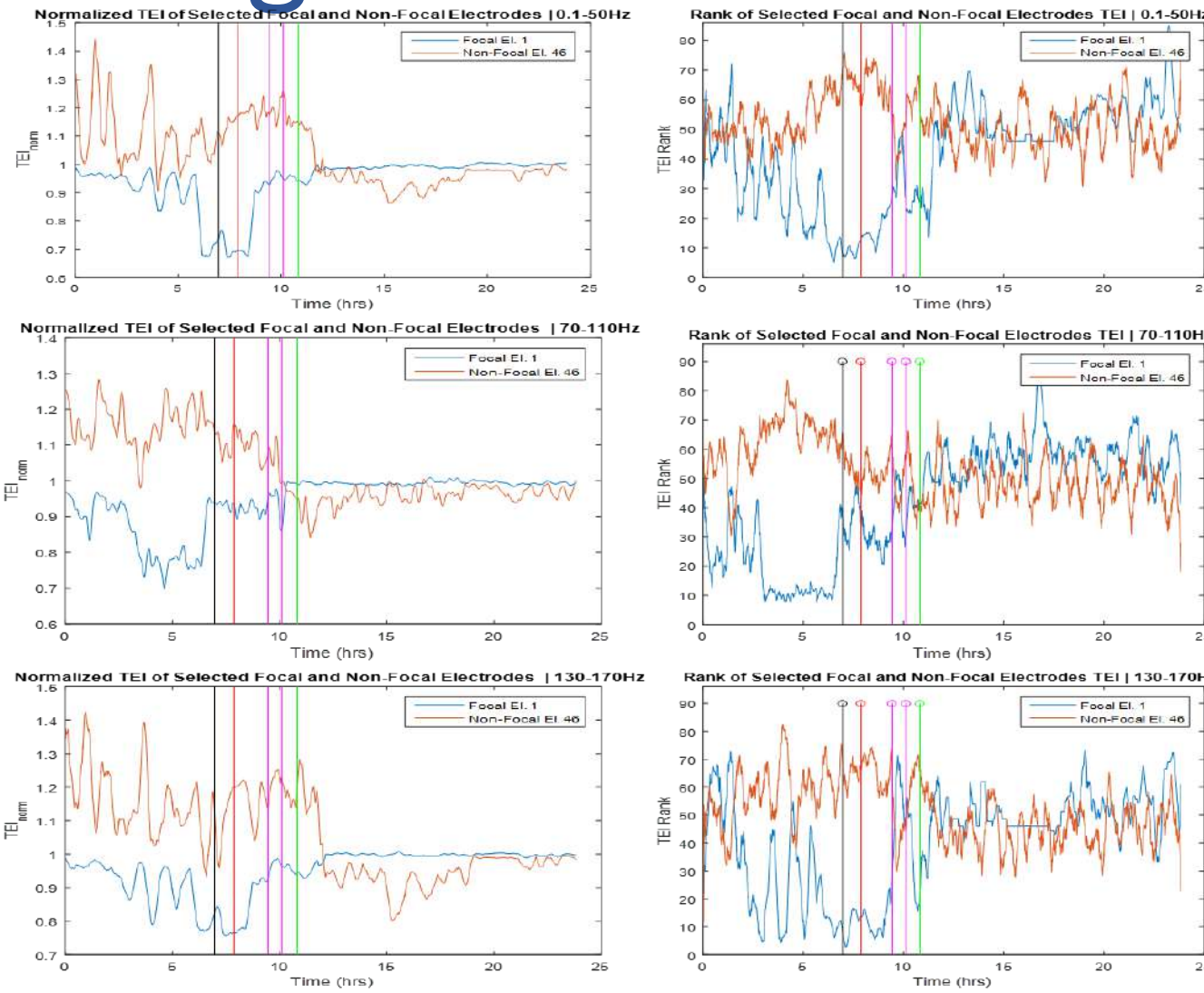
Barrow Neurological Institute

T. Hutson, D. Pizarro, S. Pati, and L. D. Iasemidis, “Predictability and resetting in a case of convulsive status epilepticus,” Front. Neurol., vol. 9, no. MAR, pp. 1–8, 2018.

Brain Connectivity through Status Epilepticus

Specific Brain Regions:

- Focal
- Non-Focal

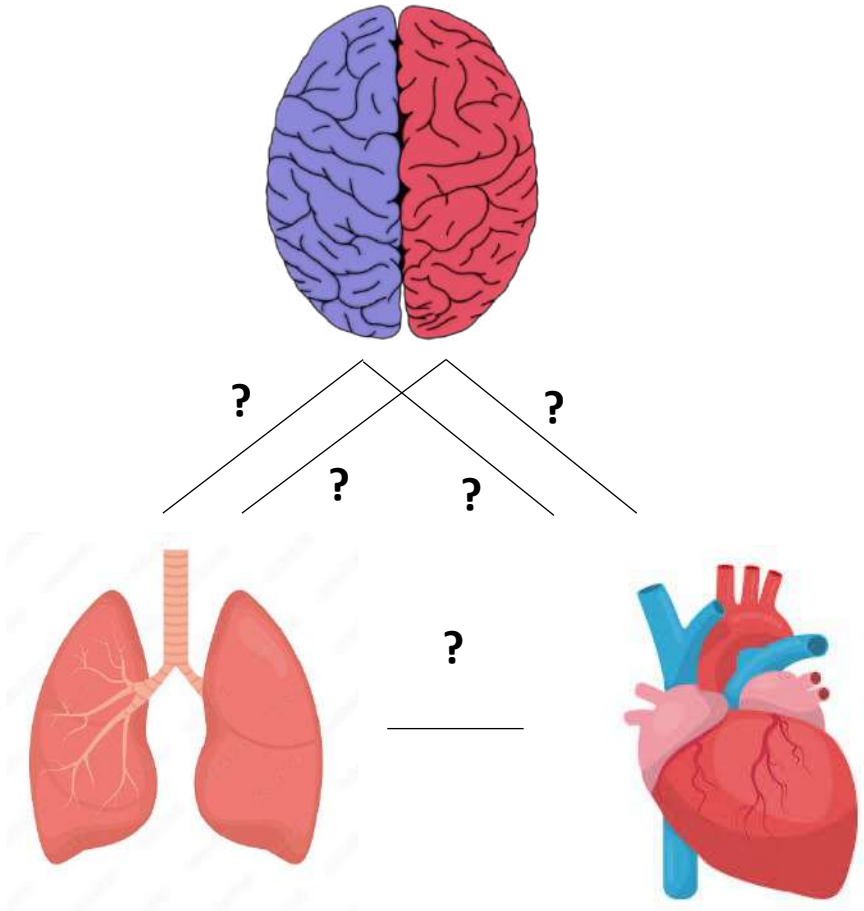


T. Hutson, D. Pizarro, S. Pati, and L. D. Iasemidis, “Predictability and resetting in a case of convulsive status epilepticus,” Front. Neurol., vol. 9, no. MAR, pp. 1–8, 2018.

Barrow Neurological Institute

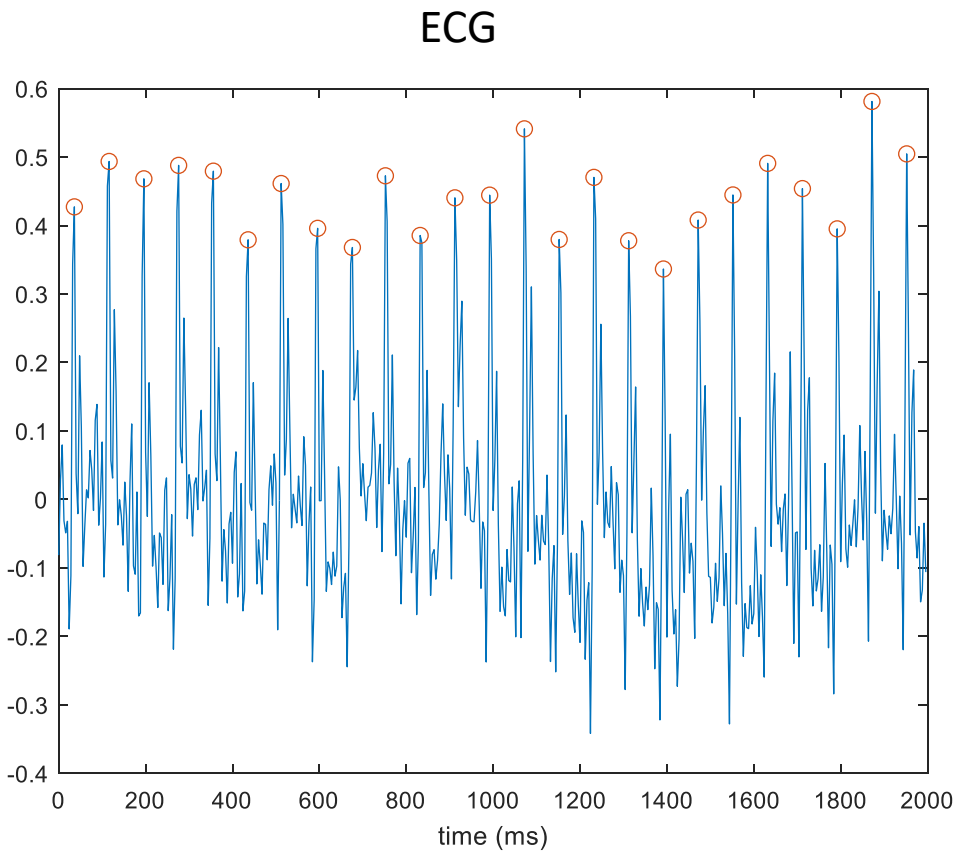
E. Brain - Heart - Lung experimental data analysis using phase synchronization

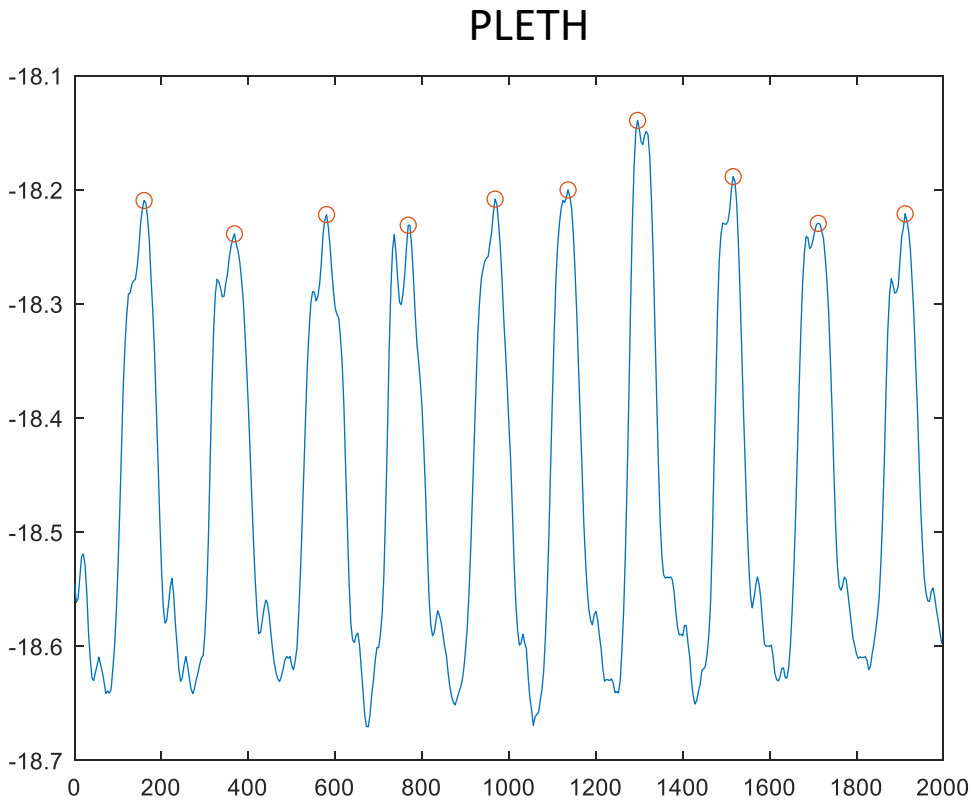
Aim: characterize network directionality



Pre-processing

- Heart rate and breath rate detection





Phase Synchronization in Brain Signals (Theory)

- Phase synchronization is the phenomenon in which waves originating in different brain areas of the same or different frequencies align their phases.
- Among the various phase synchronization metrics, the phase lag index (PLI) outperforms others because it is insensitive to volume conduction effects.
- The PLI is a quantification of the distribution of the phase difference between two EEG channels.
- Directed PLI (dPLI) quantifies the distribution of the phase difference between two EEG channels.

Hilbert transform:

$$\hat{g}(t) = \frac{1}{\pi} \int_{-\infty}^{\infty} \frac{g(\tau)}{t - \tau} \, d\tau$$

e.g. Cos(ωt)

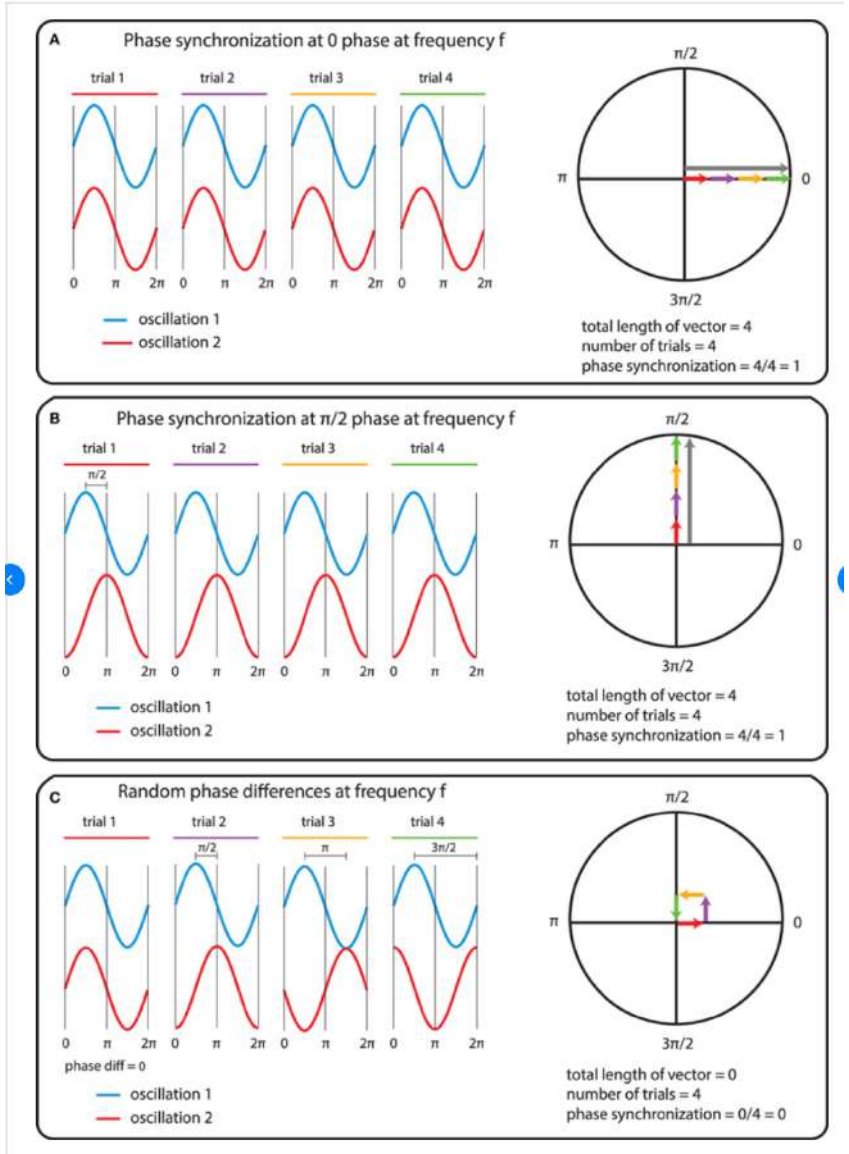
Sin(ωt) (modulo π)

Analytical Signal

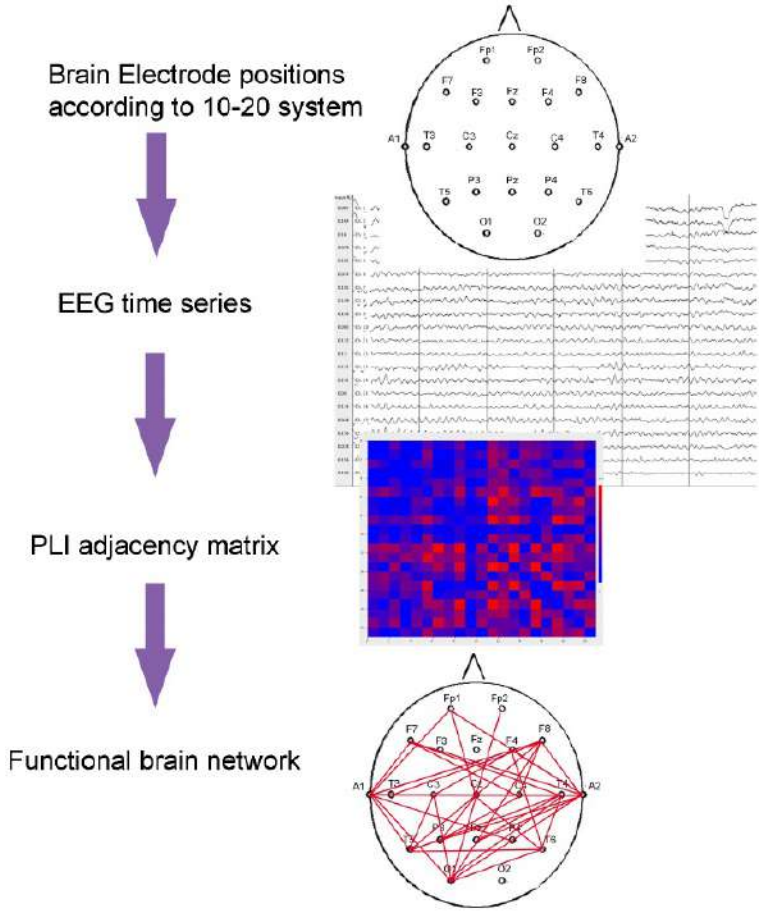
$$z(t) = x(t) + i\tilde{x}(t) = A(t)\, e^{i\phi(t)}$$

Where

$$A(t) = \sqrt{[\tilde{x}(t)]^2 + [x(t)]^2} \quad \text{and} \quad \phi(t) = \arctan\frac{\tilde{x}(t)}{x(t)}$$

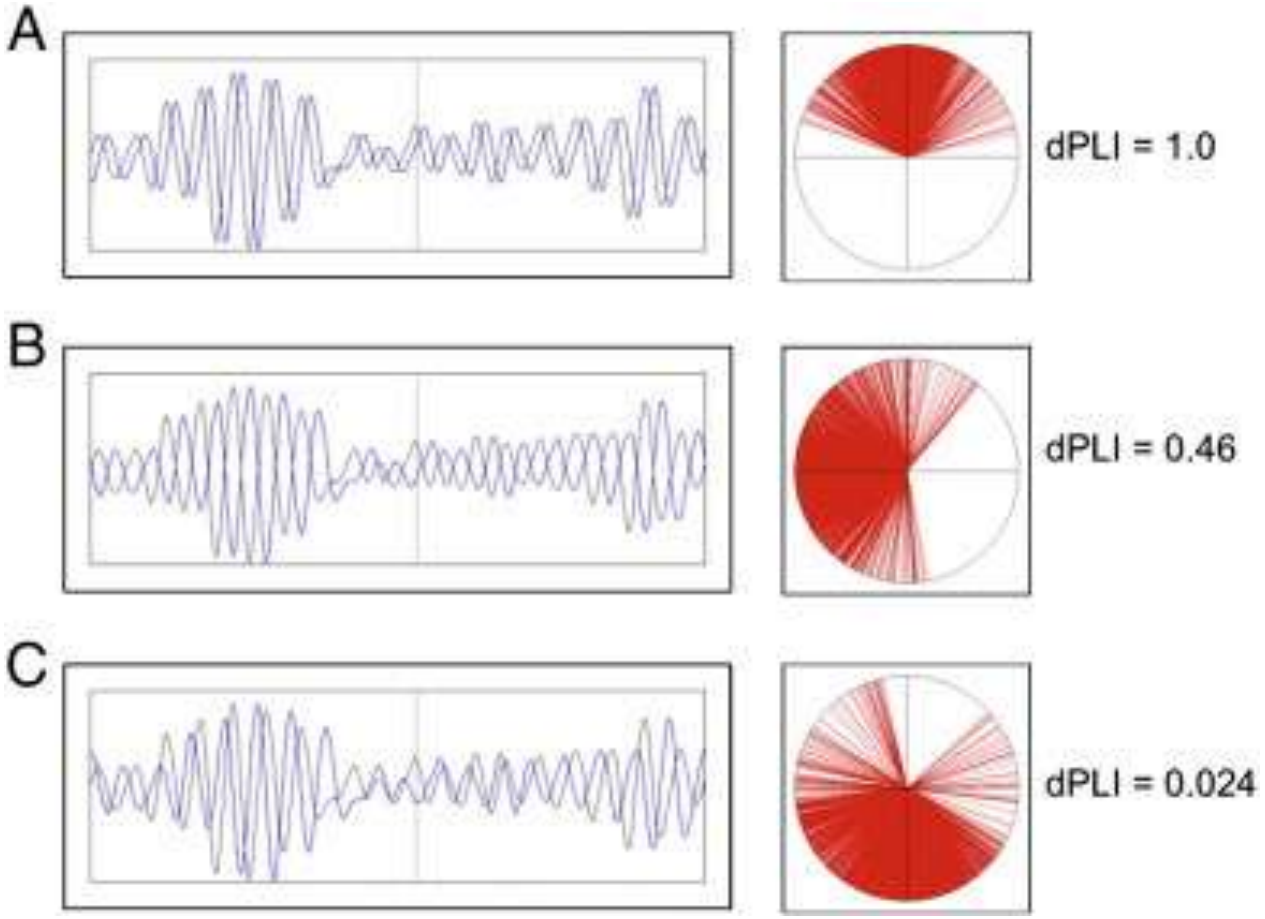


Phase Synchronization in Brain Signals (Applications)



directed phase lag index (dPLI)

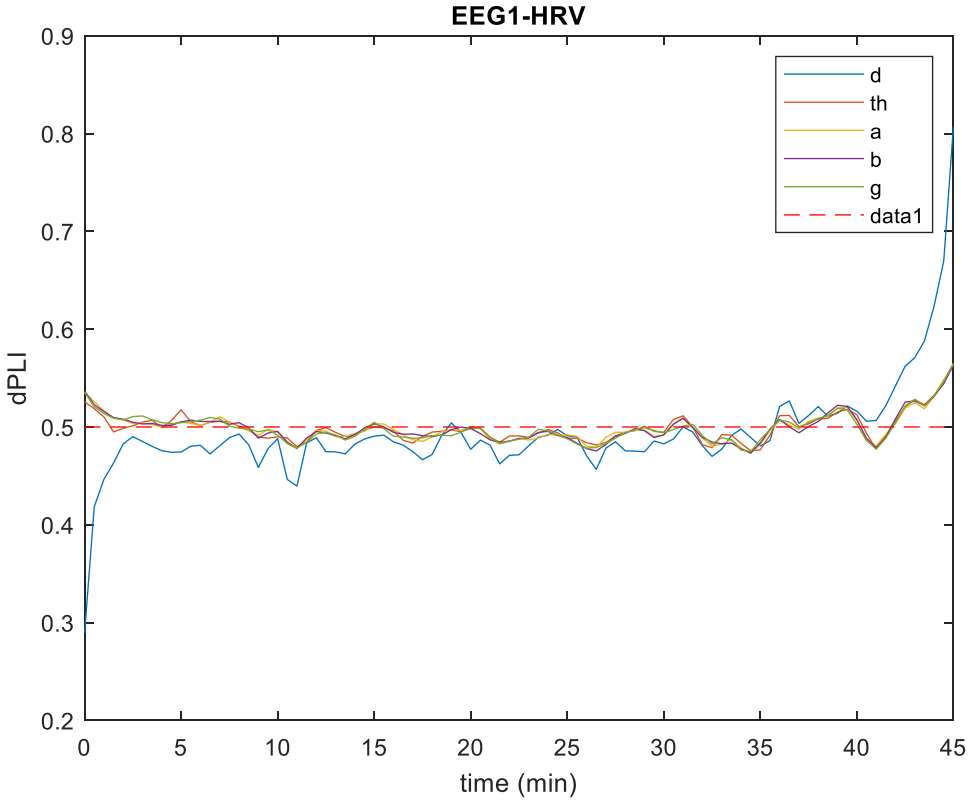
To assess both the **strength** as well as the **direction** of phase relations between signals we used directed phase lag index (dPLI) that is defined as the probability that the phase (modulo π) of one time series is smaller than the instantaneous phase of another signal.

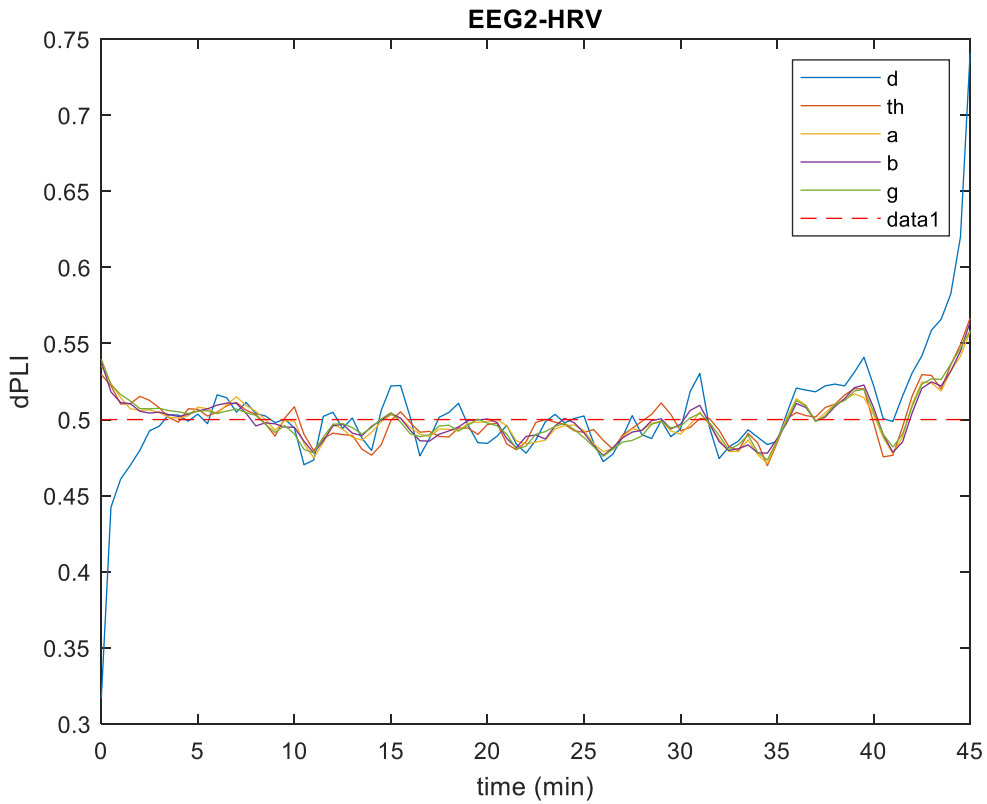


Stam, C. J., & van Straaten, E. C. (2012). Go with the flow: use of a directed phase lag index (dPLI) to characterize patterns of phase relations in a large-scale model of brain dynamics. *Neuroimage*, *62*(3), 1415-1428.

EEG-Heart Rate Variability (HRV)

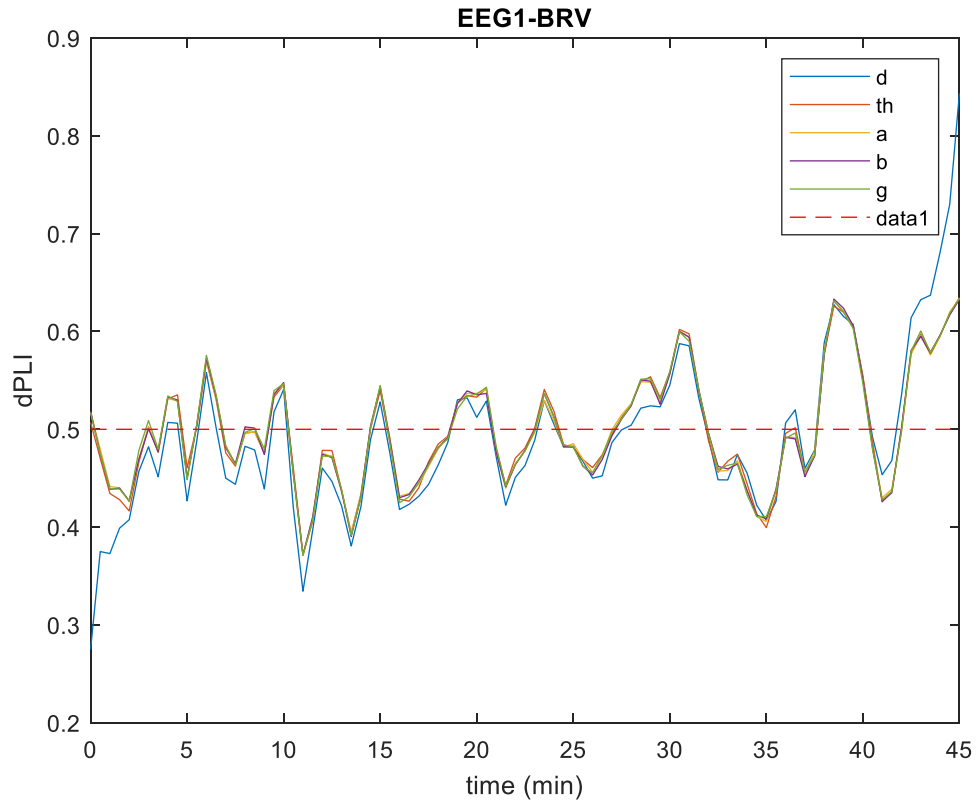
- In most time windows: **HRV→EEG**
- Inverting at end of records (mouse death?)
- Similar behavior for all frequency bands (only δ has more strength)

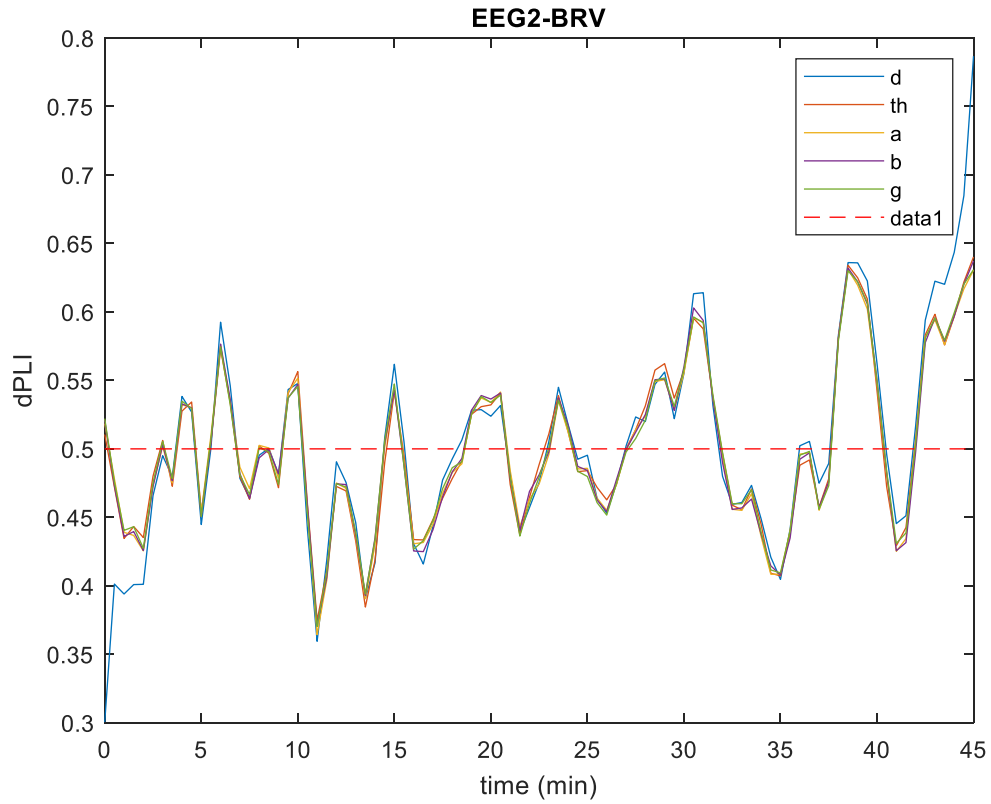




EEG-Breath Rate Variability (BRV)

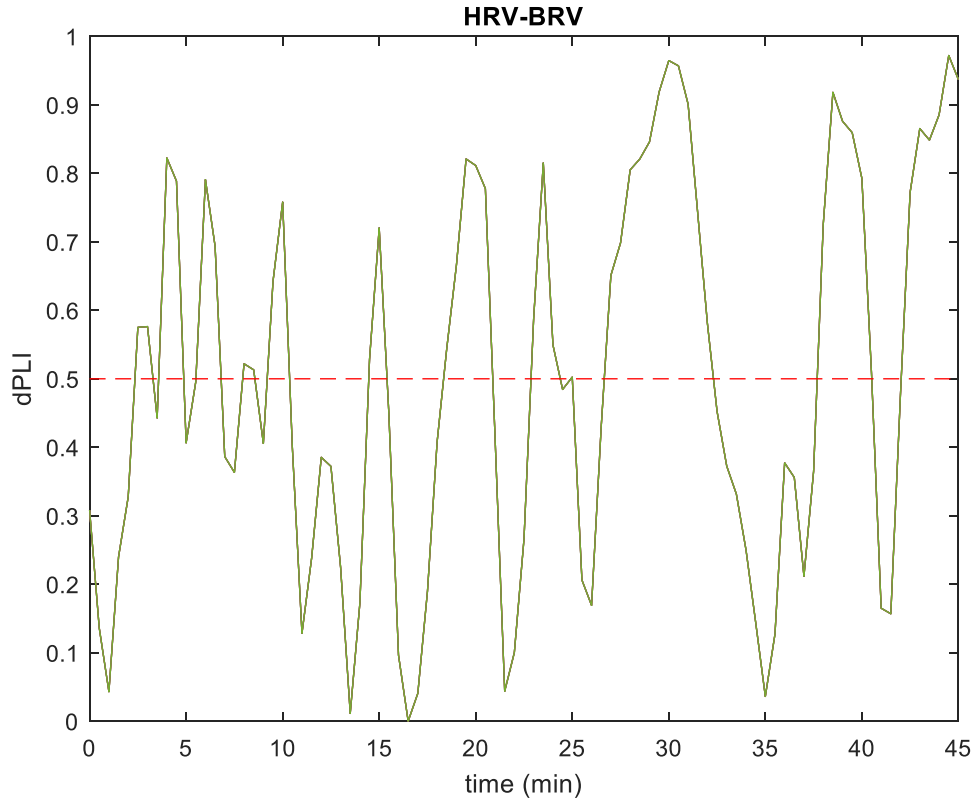
- No consistent direction (slightly more frequent BRV→EEG)
- Similar behavior for all frequency bands





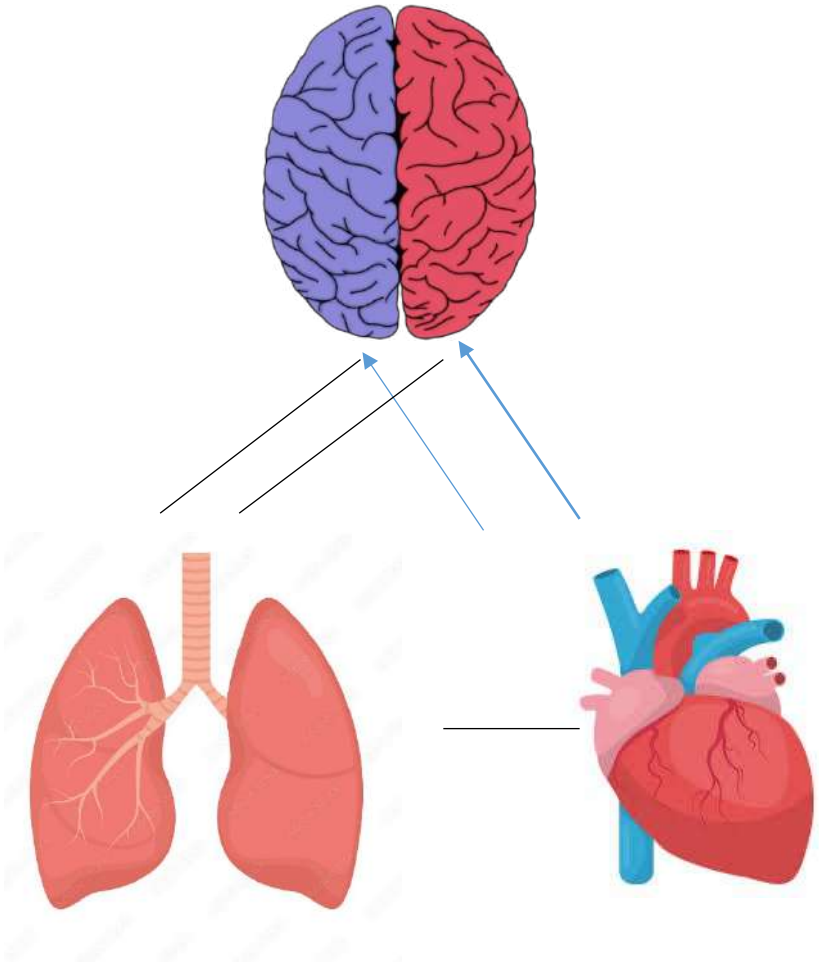
HRV-BRV

- No consistent direction
- Similar shape of HRV-BRV with EEG-BRV

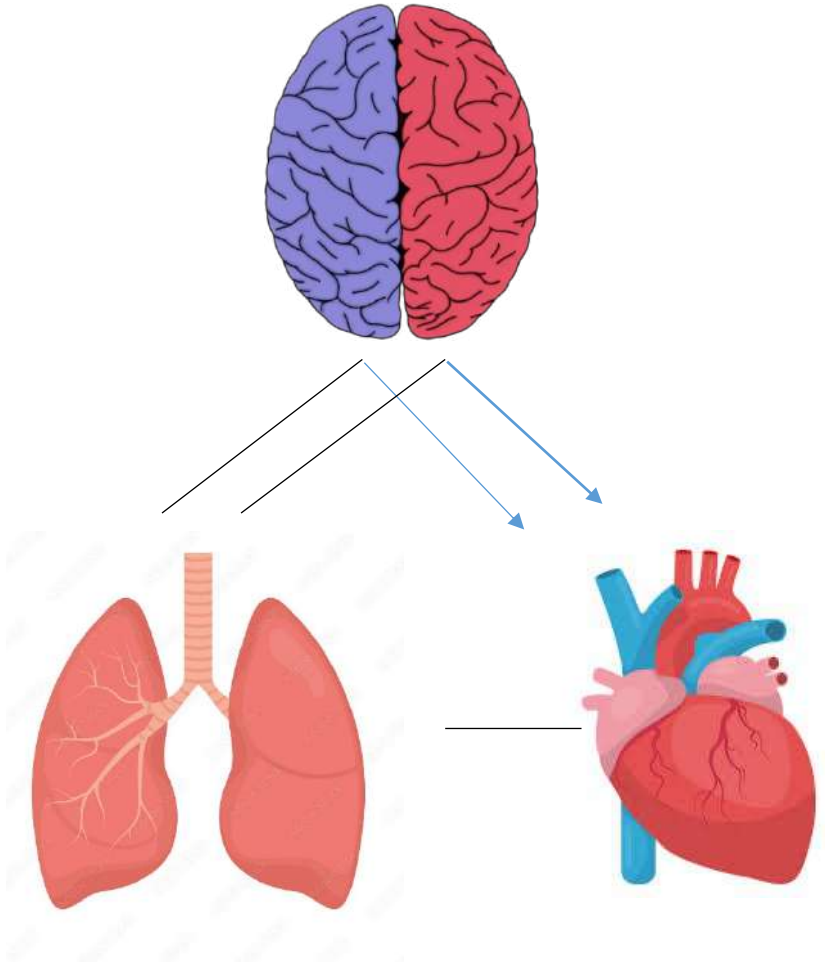


Result

Steady condition

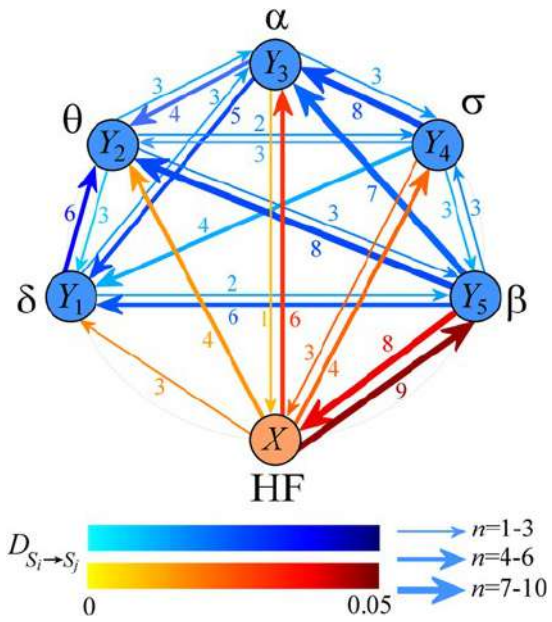


Seizures



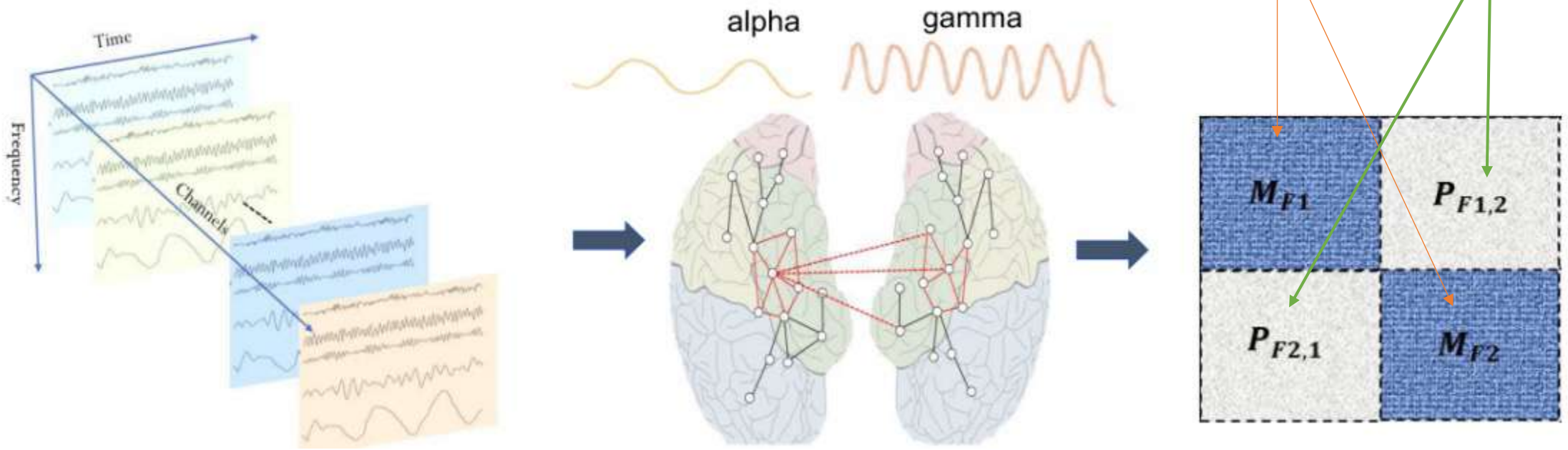
Ongoing/Future work

- Include full recording data
- Use of other derivative data (HF of HRV, LF of HRV etc)
- Compare with different methods:
  - Phase-Amplitude Coupling (PAC)
  - Cross Frequency Coupling (CFC) (For signals of different frequencies)



Ongoing/Future work: Cross-frequency coupling

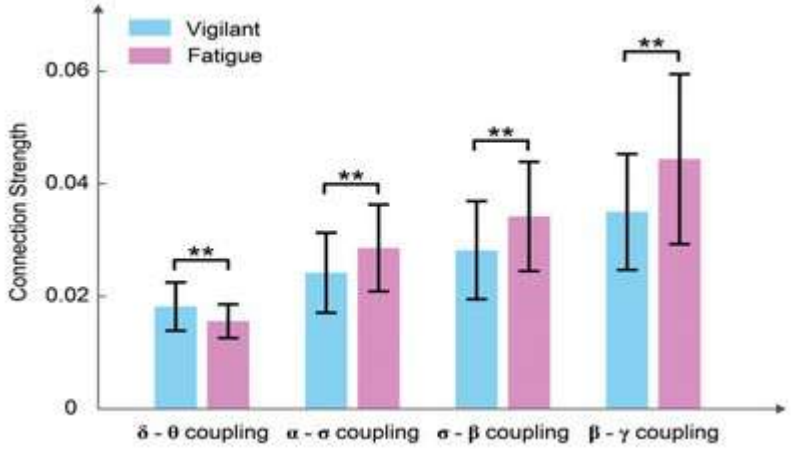
We estimated connectivity between signals of different frequencies



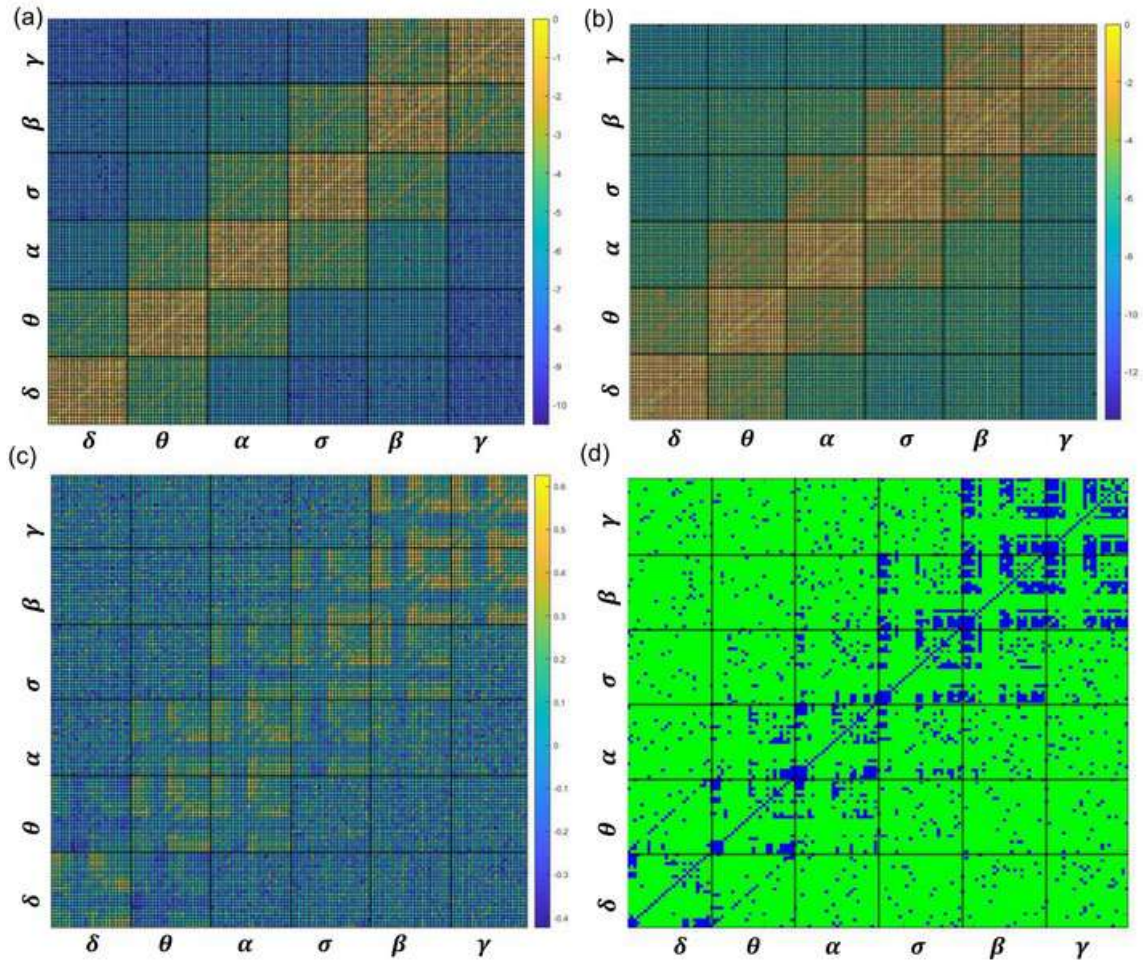
S. Liu *et al*., "Driving Fatigue Effects on Cross-Frequency Phase Synchrony Embedding in Multilayer Brain Network," in *IEEE Transactions on Instrumentation and Measurement*, vol. 72, pp. 1-14, 2023, Art no. 4005614

Ongoing/Future work: Cross-frequency couplin

- Indicative results in mental workload



CFC between two frequency layers.

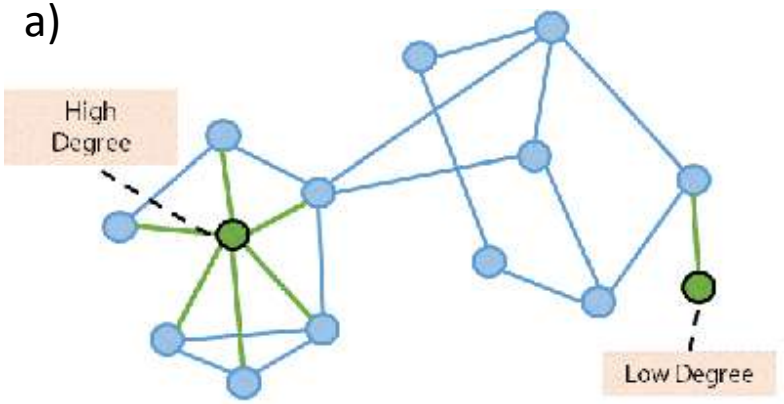


Visualization of CFC. The adjacency matrix (logarithmic form) of full multilayer brain networks for a typical subject in **(a) vigilant** and **(b) fatigue** states. **(c) Difference** in the CFC strength between vigilant and fatigue states. **(d) Blue** indicates a **significant difference** in connectivity level ($p < 0.05$, corrected for multiple comparisons).

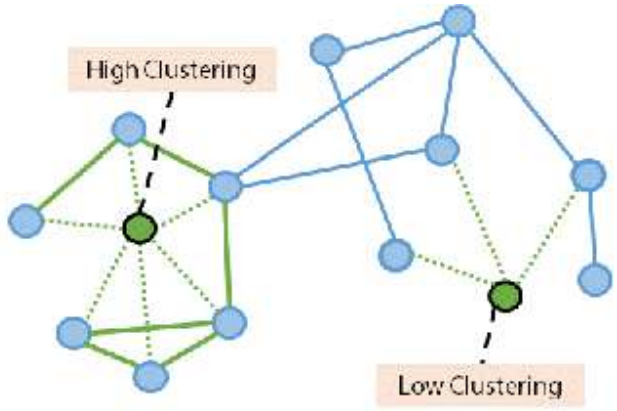
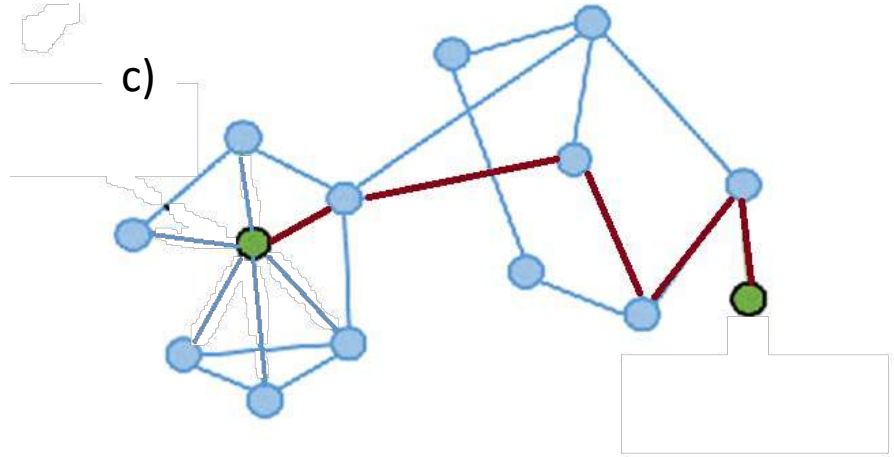
Ongoing/Future work

- Estimate connectivity measures over time, e.g.:
  a) Degree
  b) Clustering coefficient
  c) Path length / efficiency

a)



b)



c)