Epilepsy, Respiration, and Cortical Excitability

Martina Saltafossi[1,2], Teresa Berther[1,2], Gian Marco Duma[3], Simone Cuozzo[3], Luc Wilson[4], Paolo Bonanni[3], Joachim Gross[1,2], Daniel S. Kluger[1,2]

[1]Institute for Biomagnetism and Biosignal Analysis, University of Münster, Münster, Germany
[2]Otto Creutzfeldt Center for Cognitive and Behavioral Neuroscience, University of Münster, Münster, Germany
[3]Scientific Institute IRCCS E. Medea, Epilepsy and Clinical Neurophysiology Unit, Conegliano, Italy
[4]McConnell Brain Imaging Centre, Montréal Neurological Institute, McGill University, Montréal, Canada

Background

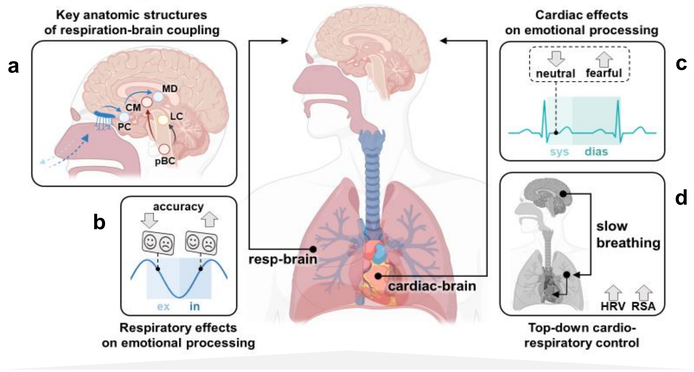


Fig. 1. Respiratory coupling to brain function and behaviour[1]. a, Nasal respiration activates olfactory bulb mechanoreceptors, shaping neural oscillations, while brainstem generators regulate arousal via the thalamus and locus coeruleus[2,3] **b & c,** Respiratory and cardiac phases influence sensory[4,5] and emotional processing[6,7]. **d,** Respiration serves as a crucial physiological modulator, as it can control the (para)sympathethic tone through respiratory sinus arrhythmia[8].

- Respiration drives neural signaling by modulating both oscillatory and non-oscillatory (1/f slope) dynamics[9]
- Epilepsy often involves dysregulation of excitation-inhibition (E:I) balance, reflected in alteration of the 1/f slope[10,11]
- A case report on focal epilepsy demonstarted respiration phase-locked shifts of E:I balance and their role in the timing of intercital epileptiform discharges[12]
- <u>The extent to which respiration affects cortical excitability and oscillatory activity in a larger epilepsy cohort remains unclear</u>

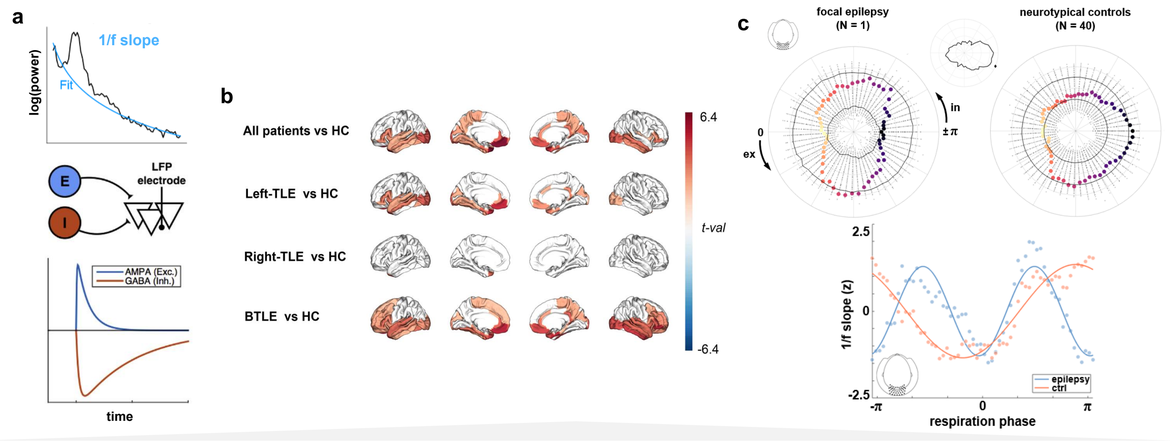


Fig. 2. E:I balance, epilepsy and their link to respiration. a, The 1/f spectral slope of the electrophysiological power spectrum, representing the non-oscillatory, scale-free component of neural activity, relates to cognitive and perceptual states. It reflects synaptic current integration, with excitatory currents producing a flatter PSD and inhibitory currents resulting in a steeper PSD, depending on their relative dominance[13,14]. **b,** Patients with temporal lobe epilepsy exhibit a larger aperiodic exponent (i.e., E < I), primarily localised in the temporal, dorsal-frontal, and cingulate regions of the brain[11]. **c,** Changes in the 1/f slope are phase-locked to respiration in both epilepsy and neurotypical population. However, in epilepsy, this relationship appears to function differently, potentially reflecting altered neural dynamics associated with the disorder[12].

Methods

Epilepsy patients

- The majority of the clinical sample consists of patients with focal and bilateral TLE, followed by those with FLE and OLE
- Detailed clinical information, including epilepsy type, age of onset, current age, medication, sex, and other relevant factors, will be available soon and will inform the analyses

Data acquisition

- Long-term video-EEG monitoring with cardio-respiratory polygraphy
- Low-density EEG: N channels = 15 - 29
- Respiration via abdominal belt
- 1 hour of resting state -like data extracted (before sleep)

Preprocessing and analyses

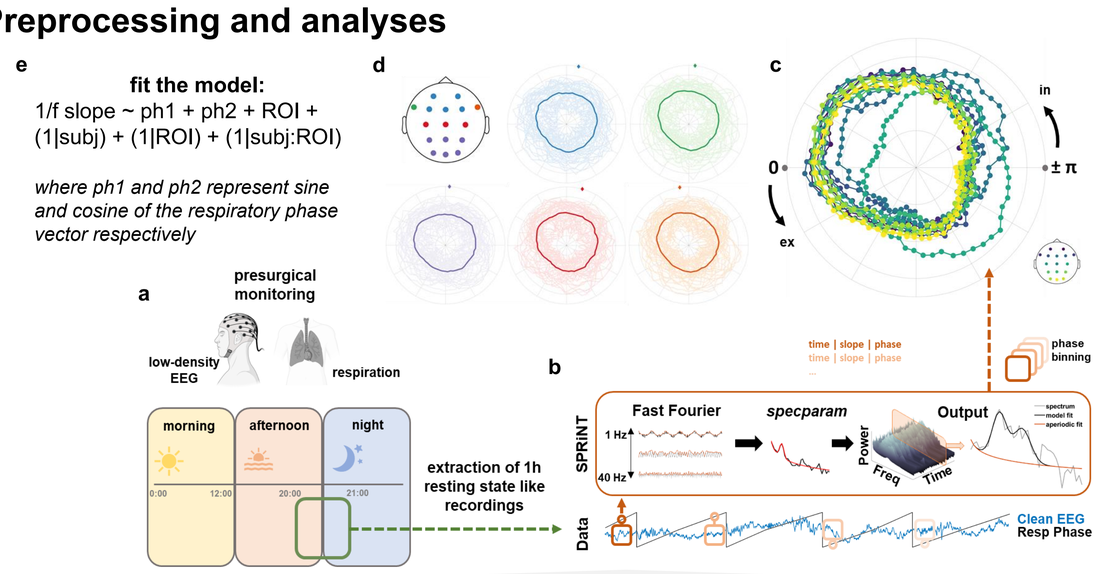


Fig. 3. Methods synopsis 1/f slope ~ respiration. a, 1 hour of interictal EEG and peripheral signals were extracted from long-term monitoring. **b,** After cleaning the data, single channel time series were subjected to the SPRiNT algorithm[15]. Using a moving window, estimates of the aperiodic component of the Fourier-transformed neural data are obtained every 250ms. For each moving-window centre, the corresponding respiratory phase was extracted. This yielded quasi-continuous, respiration phase-resolved courses of 1/f slope per channel[9,12]. **c & d,** Averaged phase (n = 60) -binned slopes are computed for each channel and for each ROIs (e.g. lobes) per patient. **e,** Linear mixed effect models (LMEM) will be employed to test the influence of respiratory phase on 1/f slope.

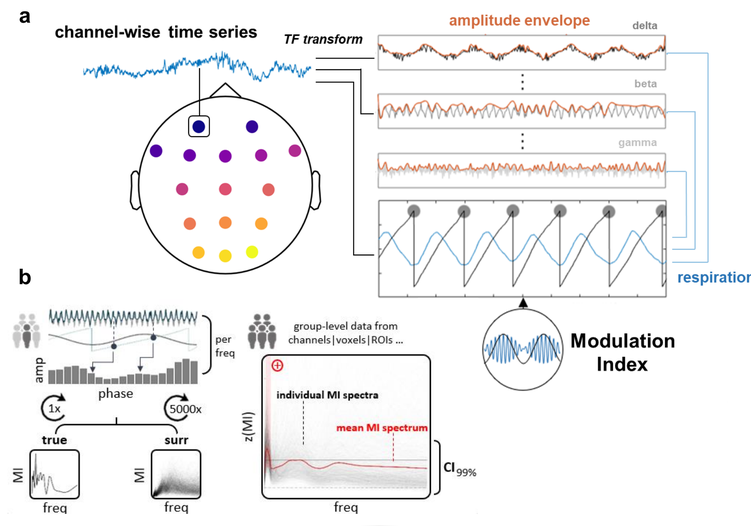


Fig. 4. Modulation Index analysis. a, MI quantifies the extent to which the amplitude envelopes of frequency-specific brain oscillations are modulated by respiration. We computed modulation indices for each channel, frequency, and patient[16]. **b,** Statistical testing for MI will involve creating k = 5000 surrogate respiration time series using the iterated amplitude-adjusted Fourier transform (IAAFT)[17]. These surrogates serve as a null distribution against which the observed MI values are compared.

Preliminary results

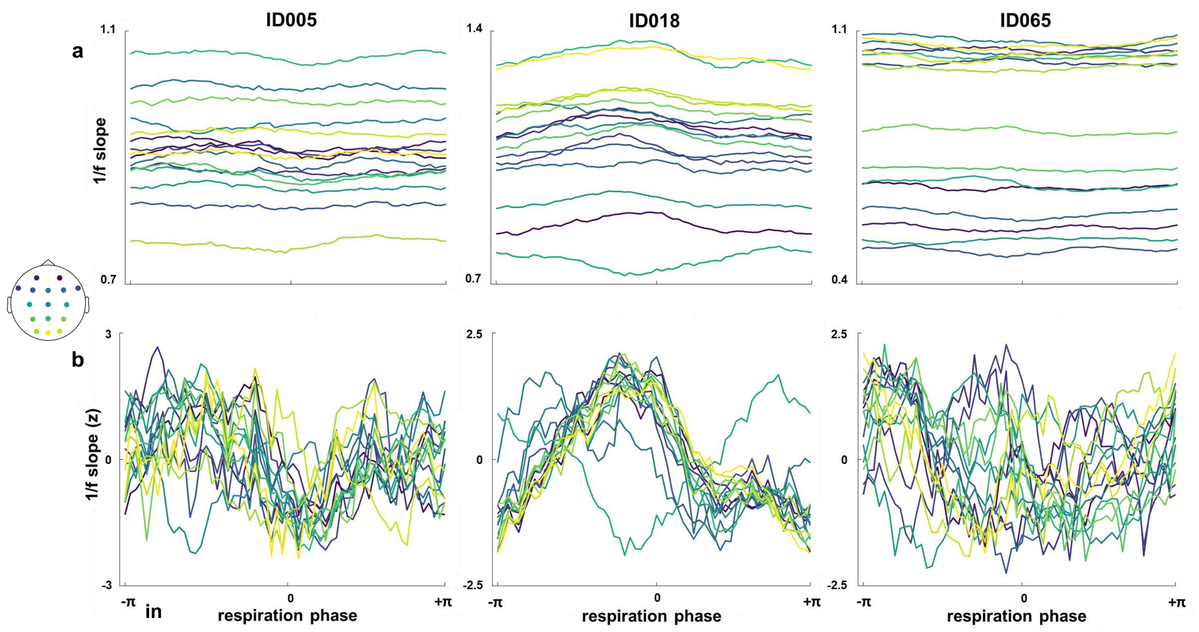


Fig. 5. 1/f slope ~ respiration per channel. a, Plots showing baseline variability across 16 channels for three exemplary patients. **b,** Corresponding plots illustrating modulation within the respiratory cycle, where the 1/f slope is normalised across phase bins. Each patient's channel layout was subsampled to a common set of 16 channels.

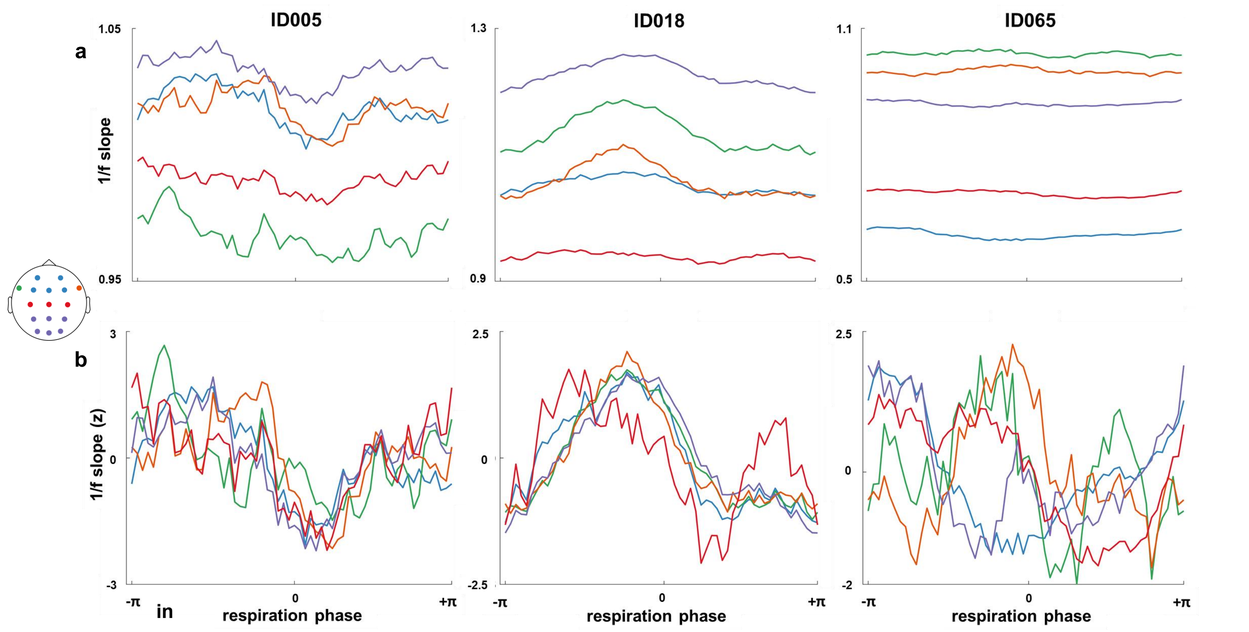


Fig. 6. 1/f slope ~ respiration per ROI. a, Plots showing baseline variability of the 1/f slope across five ROIs (frontal, left-temporal, right-temporal, central, and parieto-occipital) for three exemplary patients. **b,** Corresponding plots illustrating modulation within the respiratory cycle, with the 1/f slope normalised across phase bins. Note that here the number of channels per ROI may vary depending on the individual montage (n = 15–29).

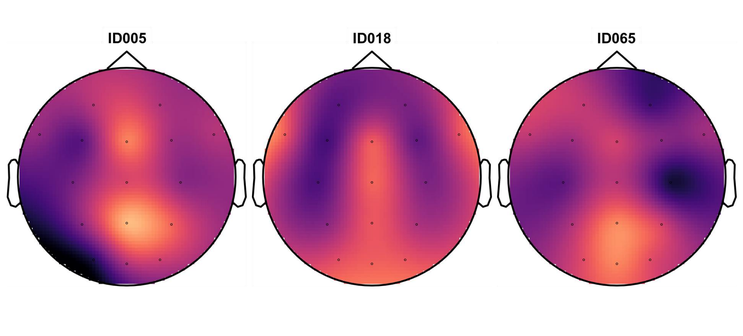
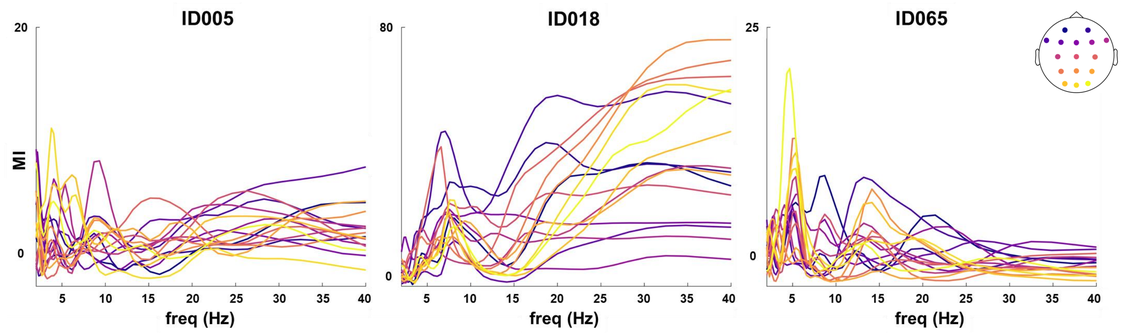


Fig. 7. Topographic organisation of E:I balance. The three topographies depict the spatial distribution of the 1/f slope, averaged across respiratory phases. Darker colours indicate greater excitability, while brighter colours reflect a shift toward inhibition.

Fig. 8. Modulation Index. Plots display MI values across frequencies (2-40 Hz) for each channel (n = 16) in three exemplary patients.



Discussion

- Power spectral phenomena (oscillatory and non-oscillatory activity) are more useful biomarkers in the interictal phase since they are ubiquitous and consistently available for quantification, in contrast to the sporadically occurring interictal epileptic discharges and seizures[18]
- These cortical dynamics are coupled to respiration in (at least) two different ways
  - phase-amplitude coupling driven by infraslow oscillations within OB[19]
  - CO_2-induced changes in tissue pH linked to excitability changes (via adenosine/ATP levels)[20-23]
- Respiratory alkalosis (i.e., elevated arterial pH) triggers hyperventilation-provoked seizures in rats and humans[24]. Additionally, altered respiratory-related brain pulsations (i.e., mechanical stimulation) may contribute to epileptic pathophysiology by disrupting CSF homeostasis and neural oscillations[25]
- <u>Future directions</u>:
  - tailor analyses to clinical data (e.g. seizure onset foci)
  - investigate brain-respiration coupling during sleep

References

1. Saltafossi et al., J Aff Dis, 2025 | **2.** Brændholt et al., NBBR, 2023 | **3.** Kluger et al., J Neurosci, 2024 | **4.** Saltafossi et al., bioRxiv, 2025 | **5.** Saltafossi et al., Biol Psychol, 2023 | **6.** Garfinkel et al., J Neurosci, 2014 | **7.** Zelano et al., J Neurosci, 2016 | **8.** Zaccaro et al., Front Hum Neursci, 2018 | **9.** Kluger et al., Nat Comm, 2023 | **10.** Van Heumen et al., Front Hum Neurosci, 2021 | **11.** Duma et al., Brain Comm, 2024 | **12.** Kluger et al., Med Comm, acc | **13.** Gao et al., NeuroImage, 2017 | **14.** Donoghue et al., Nat Neur, 2020 | **15.** Wilson et al., eLife, 2022 | **16.** Kluger et al., PLoS Biol, 2021 | **17.** Theiler et al., Physica D: Nonlin Pheno, 1992 | **18.** Latreille et al., Epilepsia, 2024 | **19.** Ito et al., Nat Comm, 2014 | **20.** Chesler, Physiol Rev, 2003 | **21.** Lee et al., Brain Res, 1996 | **22.** Ito et al., J Cereb Blood Flow Metab, 2003 | **23.** Dulla et al., Neuron, 2005 | **24.** Salvati et al., eLife, 2022 | **25.** Elabasy et al., Sci Rep, 2023

Transdiagnostic Brain-Body
Saltafossi et al., J Aff Dis 2025

Epilepsy (case study)
Kluger et al., Med Comm accepted

Further reading

Respiration & multisensory integration
Saltafossi et al., bioRxiv 2025

Cardiac phases & multisensory integration
Saltafossi et al., Biol Psychol 2023

Contact
martinasaltafossi.bsky.social
martina.saltafossi@uni-muenster.de