

Vagus Nerve Electroneurogram in Genetic Absence Epilepsy Rats from Strasbourg (GAERS)

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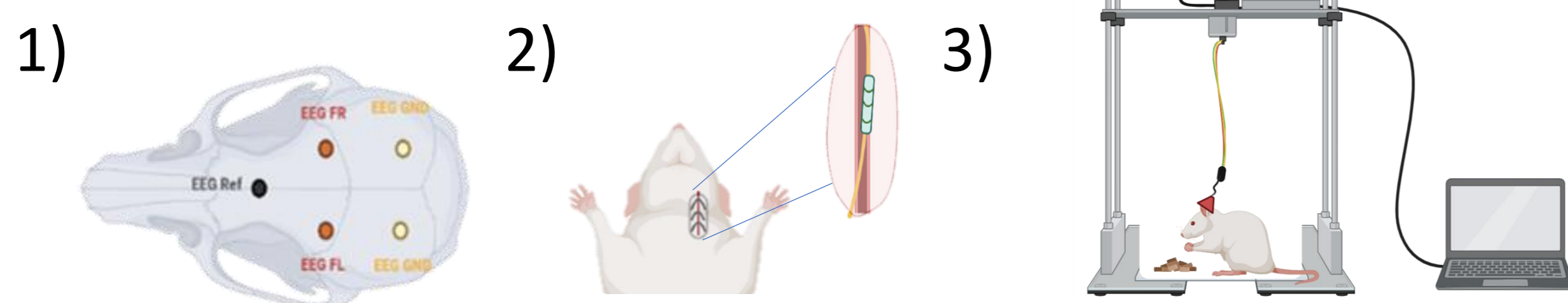
Background

- **Seizures** are associated with **autonomic symptoms** [1]
- **GAERS** is a robust animal model of **absence seizures** [2]
- Epileptic patients and GAERS have **autonomic dysfunctions** [3]
- **Vagus Nerve (VN)** transmits **parasympathetic** information [4]
- Autonomic system **might evolve** over age in GAERS [5]

- ❖ Is the vagus nerve activity modulated during absences ?
- ❖ Does this response evolve with age ?

Methodology

Animals: 2 groups of GAERS: 1) 4 months (N= 4), 2) 6 months old (N=4)
Surgery: sevoflurane 5%, maintained under 2%



- 1) **Epidural stainless-steel EEG electrodes** implantation
- 2) Vagus ElectroNeurogram (**VENG**) tripolar cuff electrode implanted around the cervical portion of the left vagus nerve
- 3) **24h recording** (EEG-VENG-Video) freely-moving rat

Analysis: The **RMS** value (root mean square) was **computed** from the envelope of the VENG signal between **baseline** of 10 sec and **seizure** segment. Only seizures during NREM sleep were taken into account.

Results:

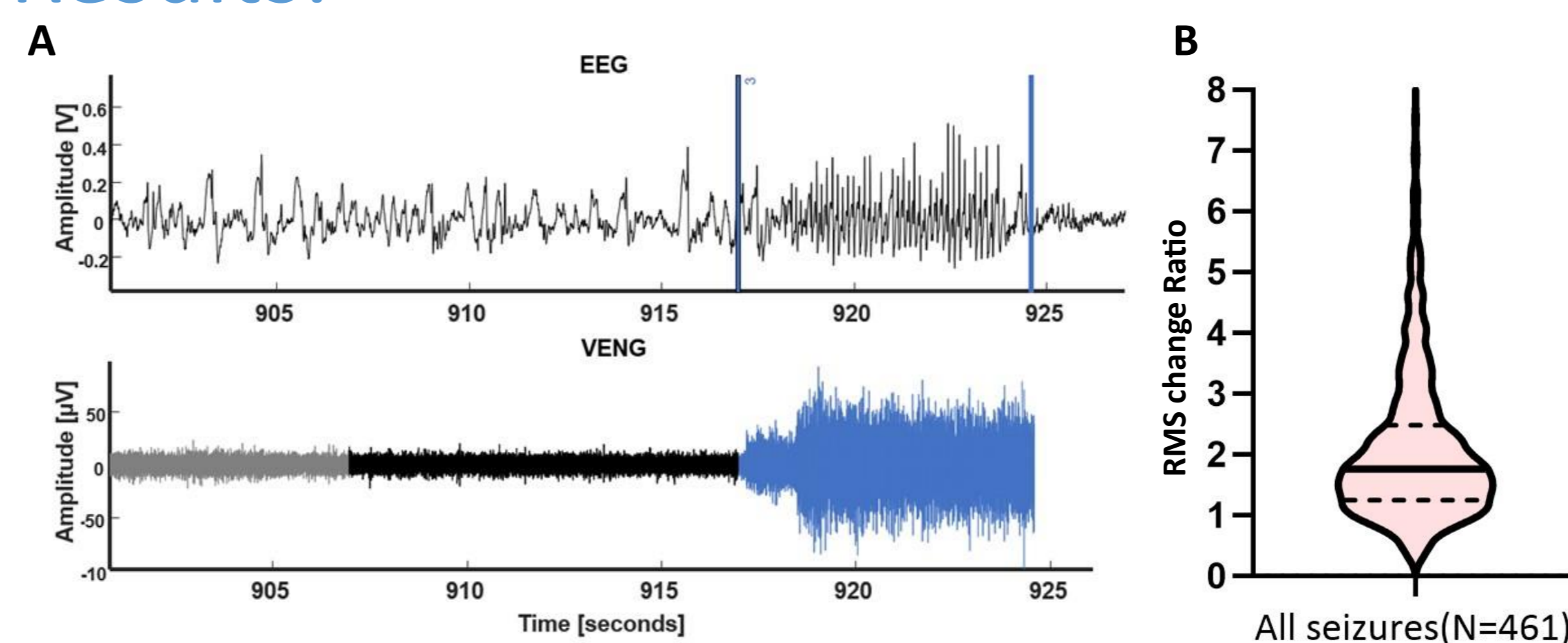


Fig 1.A. Vagus nerve activity increases during absence in GAERS. **B.** The vagus nerve activity **RMS** (root mean square) value **increased during seizure** compared to baseline in all seizures during 24h in 8 GAERS. (N=461 seizures) The median is presented with a line and the quartiles with a dash line.

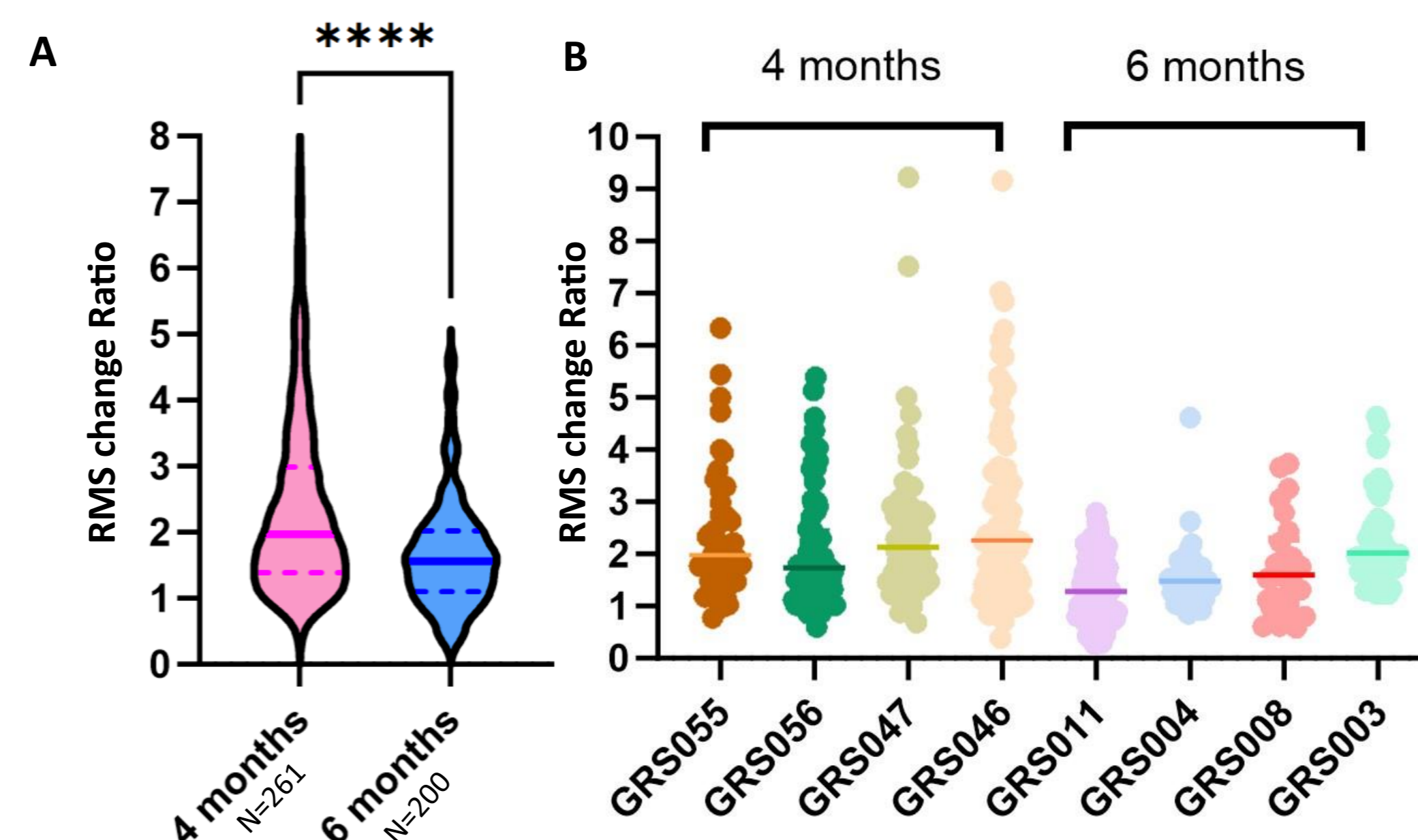


Fig 2.A. Vagus nerve activity during absence in GAERS **decreases with age**. **B.** Modulation of VN activity for each seizure (dots) per animal shows two distinct repartitions according to age. The median of each animal is presented with a line.

Conclusion

Vagus Nerve Activity chronically recorded on 8 GAERS rats (N=461 absences), show a global RMS value **increase during absences** compared to baseline during NREM sleep. The detection of this modulation could be used as a biomarker for seizure detection and development of closed loop VNS. Furthermore, the **parasympathetic response** during seizures in GAERS seems to **decrease with age**, which may reflect the evolution of **autonomic dysfunctions** with the duration of the epilepsy.

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Funding: Welbio Starting Grant

References: [1]Devinsky(2004);[2]Danober(1998);[3]Mamalyga(2014);[4]Yuan(2016);[5]Myers(2018).

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Absences modulate vagus nerve activity in Genetic Absence Epilepsy Rats from Strasbourg (GAERS)

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Key Findings

Vagus Nerve Activity increases during absences

The detection of this modulation could be used as a biomarker for seizure detection and development of closed-loop VNS.

Parasympathetic response decreases with age

Vagus nerve modulation during seizures in GAERS **decreases with age** and becomes **less variable**.

Epilepsy severity is stable throughout age in GAERS rats

Absence occurrence, duration, and main spike frequency **stay the same** between the 4, 6, and 10-month-old rats.

Thus, a decrease in vagus nerve activity during absences may reflect the evolution of autonomic dysfunctions associated with the duration of epilepsy.

Background

- 30% of epileptic patients are **refractory** to medication and not eligible to resective surgery [1]
- **VNS therapy** can be an adjunctive treatment but **1/3** of patients are **not responders** [2]
- The response can be **improved** by stimulating at the **seizure onset** [3]
- **Seizures** are associated with **autonomic symptoms** [4]
- **Vagus Nerve (VN)** transmits **parasympathetic** information [5]
- **GAERS** is a robust animal model of **absence** seizures [6]
- Epileptic patients and GAERS have **autonomic dysfunctions** [7]
- Autonomic system **might evolve** over age in GAERS [8]

- ❖ Is the vagus nerve activity modulated during absences ?
- ❖ Does this modulation evolve with age linked to seizure occurrence?

Methodology

Animals

Strain: Genetic Absence Epilepsy Rats from Strasbourg (**GAERS**)

Type of epilepsy: **Spontaneous absence** characterized by **spike and wave discharges (SWD)** between 7-11 Hz and **behavioral arrest**.

Number: **4 per group** aged of 1) **4 months**, 2) **6 months** and **10 months**

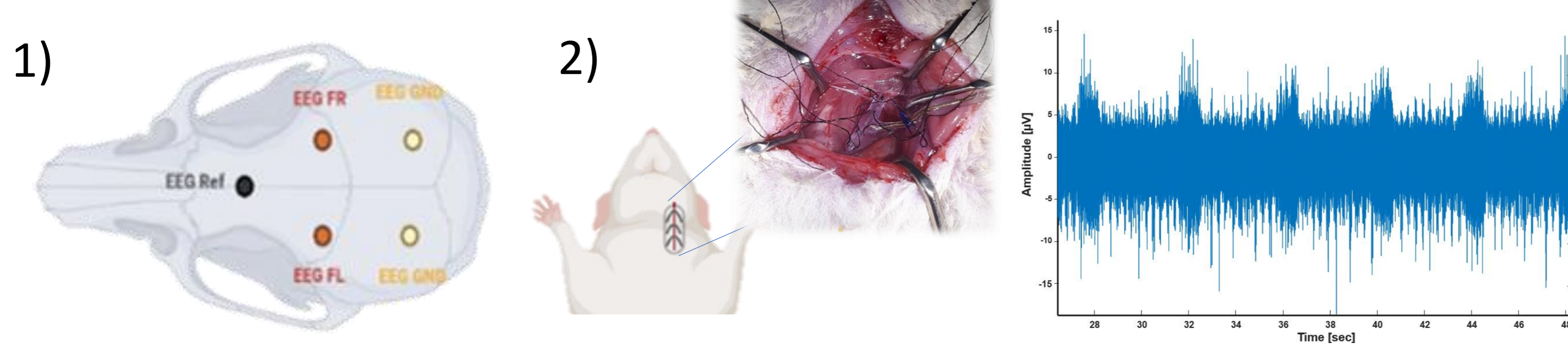
Surgery

Anesthesia: **Sevoflurane 5%**, maintained under 2%

Procedures:

1) **Epidural stainless-steel EEG electrodes** implantation

2) Vagus ElectroNeurogram (**VENG**) **tripolar cuff electrode** implanted around the cervical portion of the left vagus nerve and signal checking



Recording

After 3-4 days of recovery post-surgery, each rat is placed in a recording where he has access to food and water *ad libitum*.

3) Each rat **freely moving** is continuously recorded (**EEG-VENG-video**) for **48 hours**.

Analysis

The **RMS** (root mean square) value was **computed** from the envelope of the VENG signal between **baseline** of 10 sec NREM sleep and **seizure** segment.

Statistics

Normality was checked with Shapiro-Wilcoxon Test. Median, 25% percentile and 75% percentile of RMS VENG ratio for each rat were calculated. The difference between groups age was analyzed with a Kruskal Wallis Test analysis and multiple comparisons were corrected with a Dunn's test.



Results:

I) Epilepsy Characterization

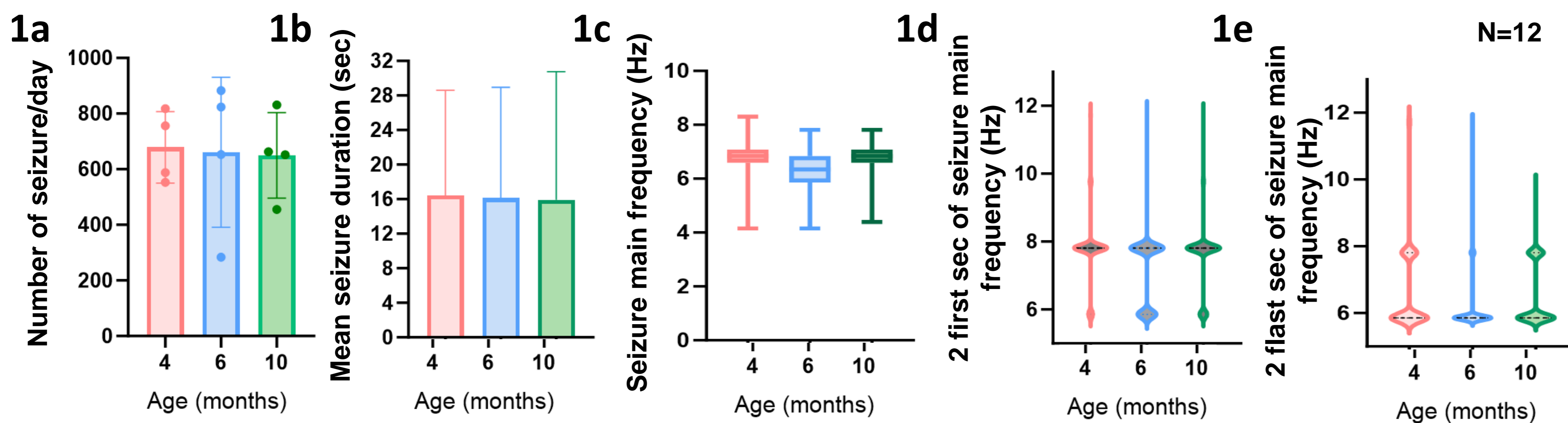


Fig 1. Evolution of absences in different age groups (N=9429 SWDs). The EEG of 12 rats has been computed. They were grouped by 4 based on their age: 4 months (pink), 6 months (blue), and 10 months (green). **A) The number of seizure per day** showed the same results between age with a mean around 650 absences per day. **B) The seizure duration in seconds** showed a mean duration equal for the three age: 16 seconds. **C) The main frequency component in Hz** calculated on the whole seizure duration showed a median that was not statistically different between ages: ≈ 7 Hz. **The main frequency component in Hz is calculated on the 2 first seconds (D) and 2 last seconds (E) of each seizure.** No differences have been shown between groups.

Epilepsy severity is stable throughout age in GAERS rats

II) Vagus Nerve is modulated by Seizures and age

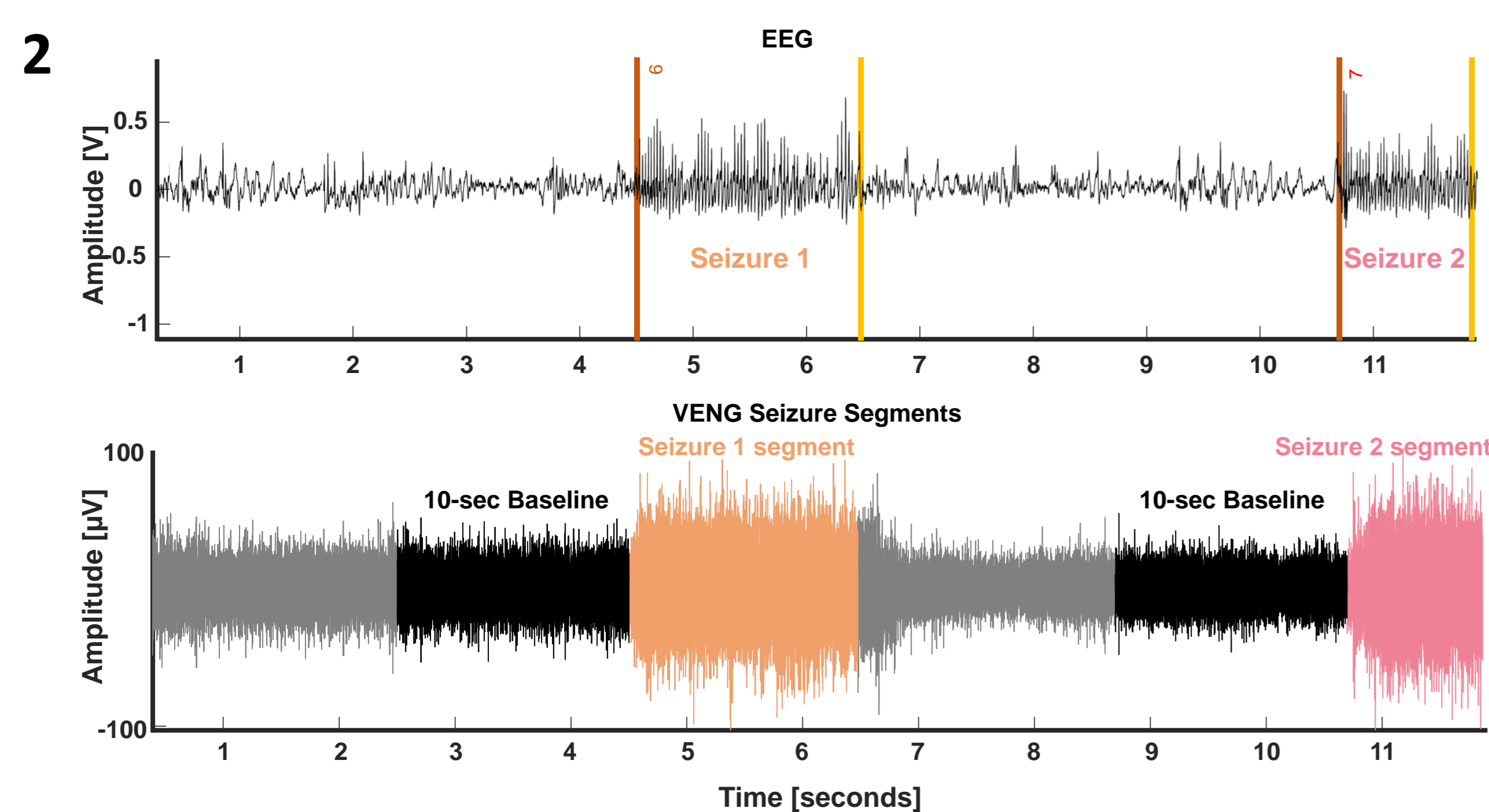


Figure 2. Vagus Nerve Activity is modulated during absences in GAERS freely moving rats. VENG increases during absence in GAERS. Upper trace: bilateral epidural EEG recording. The onsets are shown by a red line and the offsets by an orange line. Lower trace: bipolar VENG recording. The colored vagus nerve activity corresponds to the seizures detected on the EEG. The black segment is the pre-ictal phase selected as a baseline of 10 seconds.

Vagus Nerve Activity increases during absences

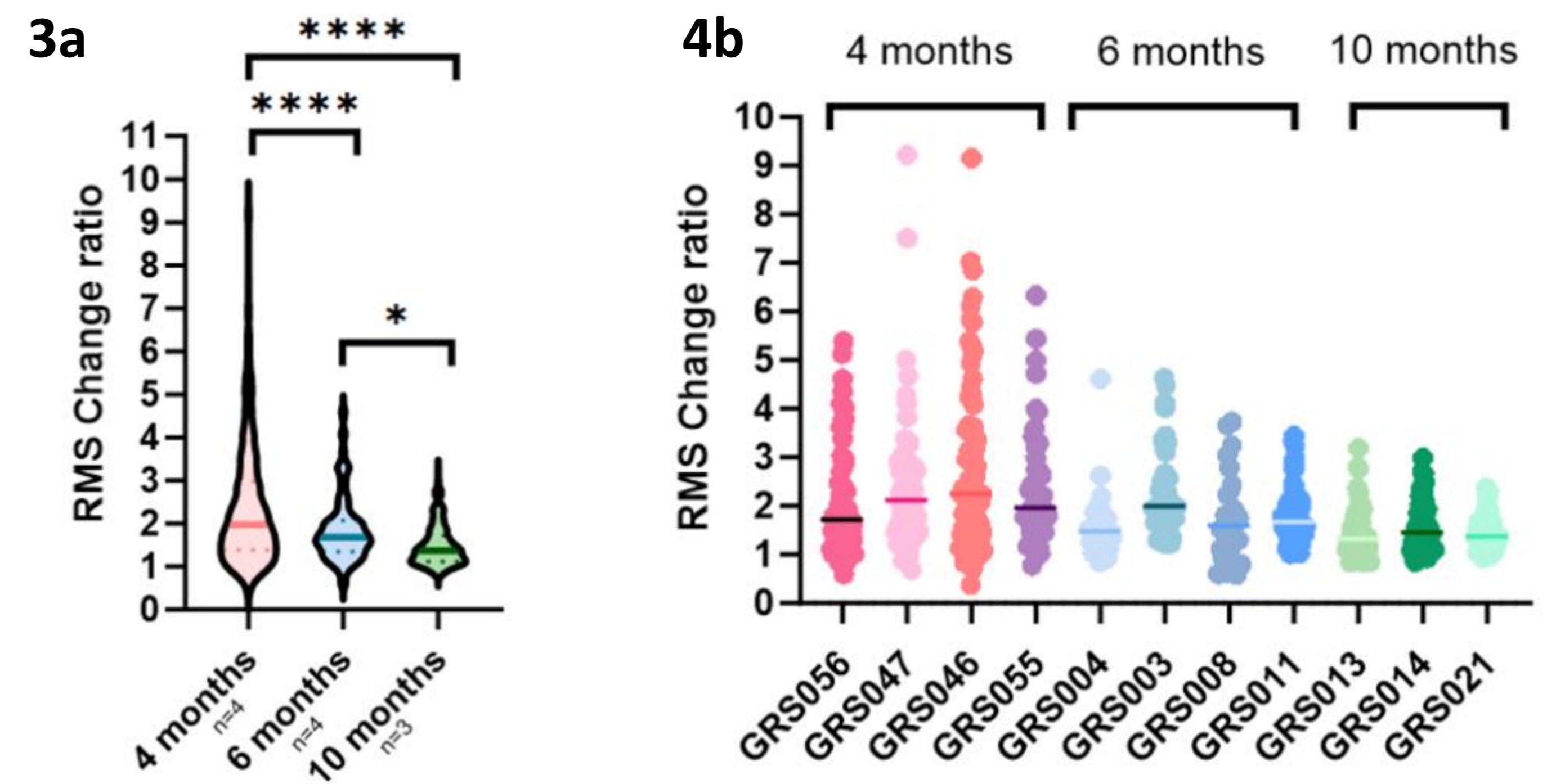


Fig 3. VENG decreases during absence with age. **A)** The RMS ratio of each seizure detected is presented pooled per group of age. The line for each violin represents the median value. The dashed lines represent the quartiles. **Vagus nerve activity** during absence in GAERS **decreases with age.** **B)** The dots representing vagus nerve modulation for each seizure per animal show a bigger variability between seizures in the 4-months rats rather than the 6 and 10-months. The median of each animal is presented with a line.

Parasympathetic response decreases with age

Conclusion: Vagus nerve activity is increased during absences which could be used for seizure detection and then closed-loop VNS. Furthermore, parasympathetic increases visible in all rats are diminished with age despite a stable severity of epilepsy revealing a potential deregulation of the autonomic system,

Methodologies for Vagus ElectroNeuroGram (VENG) analysis

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Background

➤ Vagus Nerve Activity increases during absences

The detection of this modulation could be used as a biomarker for seizure detection and development of closed-loop VNS.

➤ Parasympathetic response decreases with age

Vagus nerve modulation during seizures in GAERS **decreases with age** and becomes **less variable**.

➤ Epilepsy severity is stable throughout age in GAERS rats

Absence occurrence, duration, and main spike frequency **stay the same** between the 4, 6, and 10-month-old rats.

Thus, a decrease in vagus nerve activity during absences may reflect the evolution of autonomic dysfunctions associated with the duration of epilepsy.

Methodology

Root Mean Square analysis

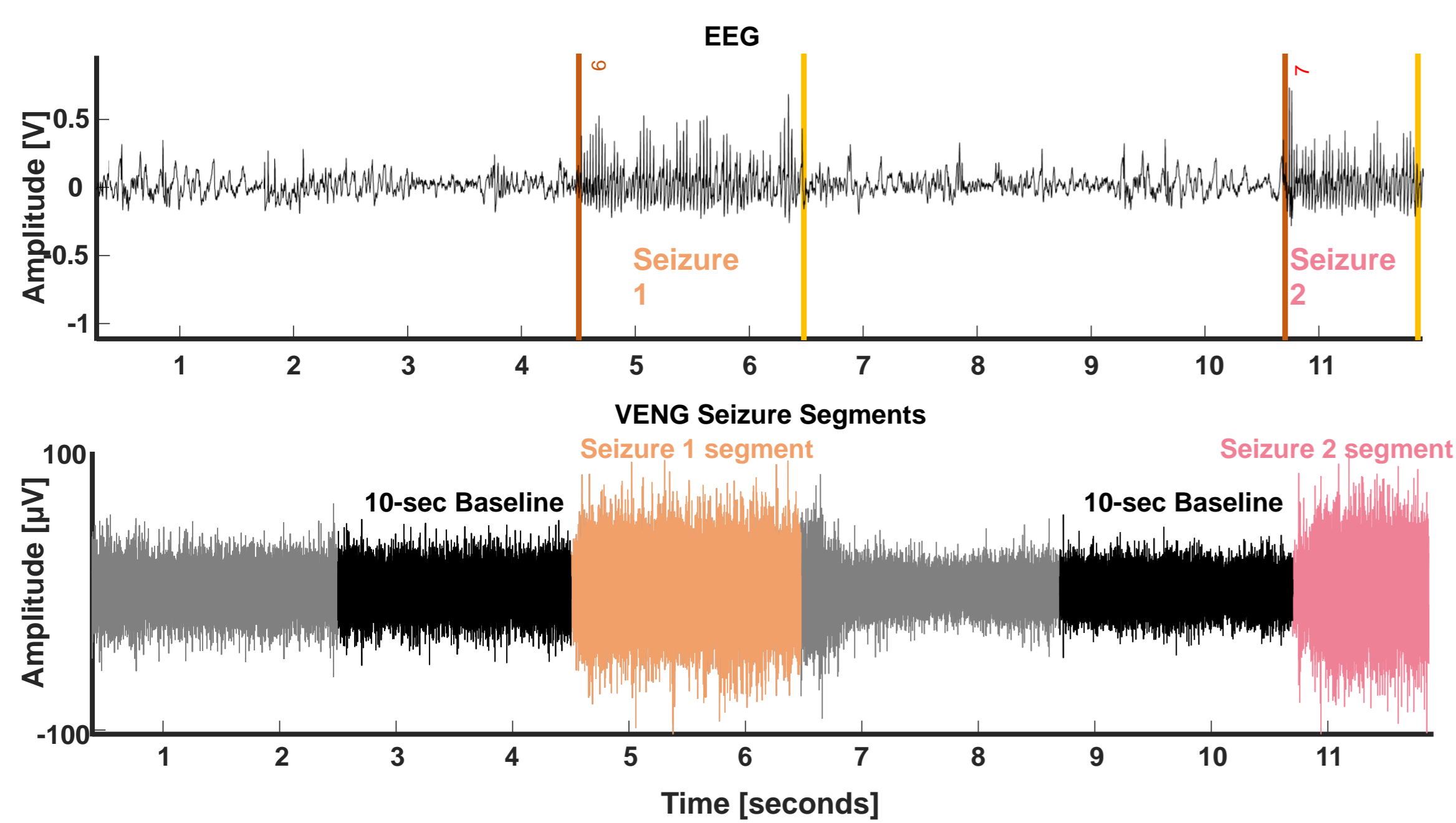


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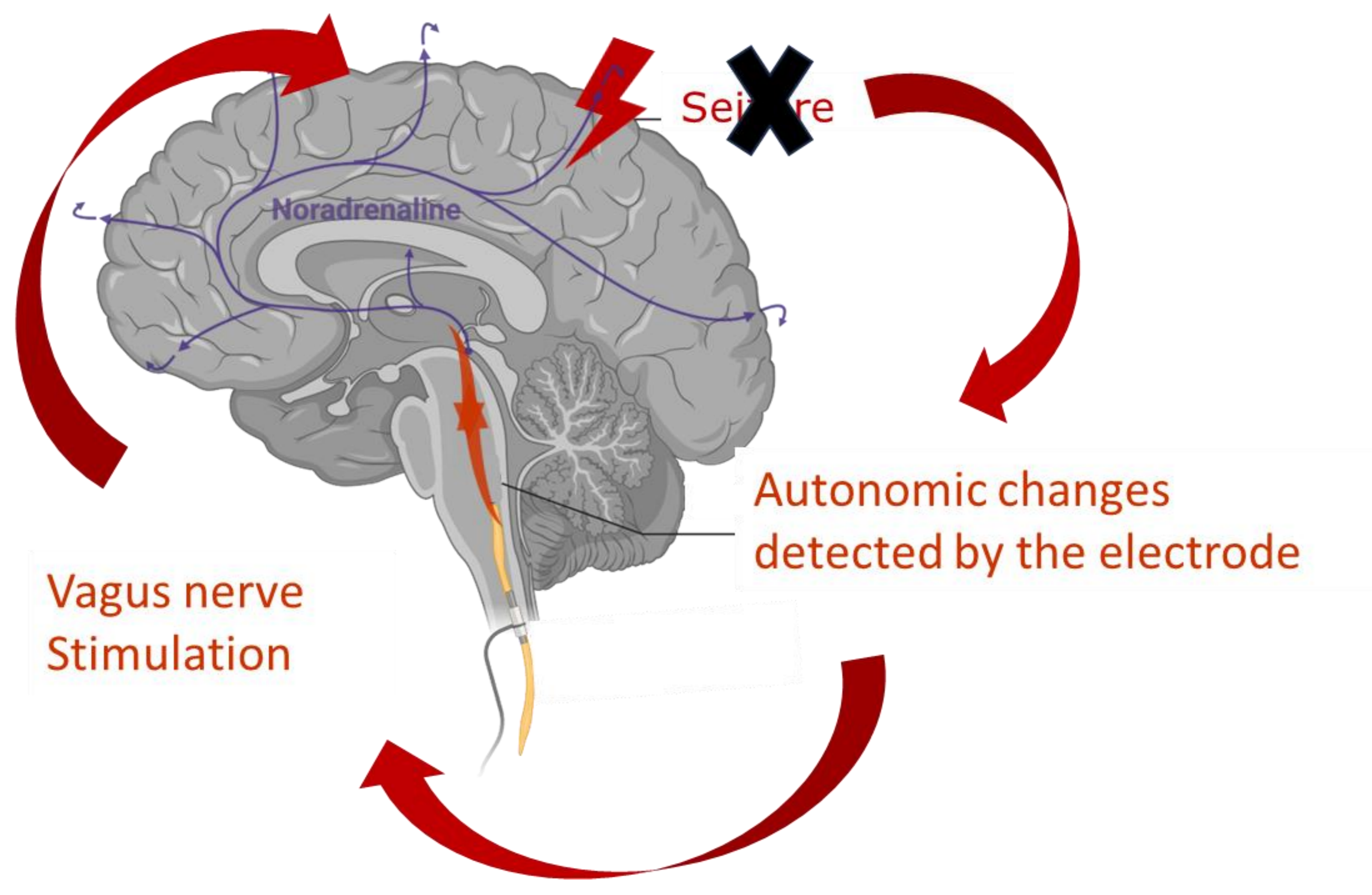
➤ Vagus Nerve Activity increases during absences

Spike Frequency analysis

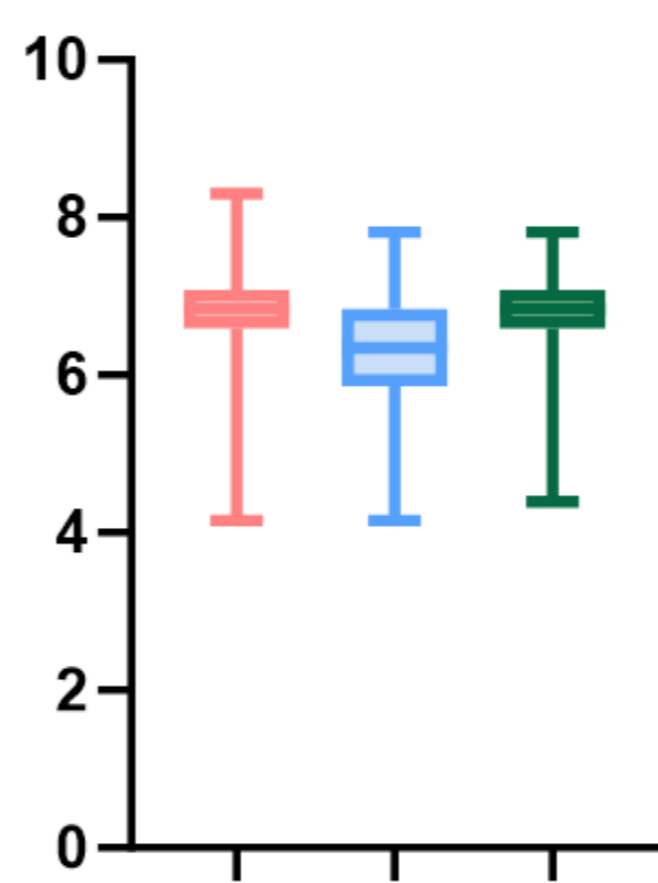
Spike sorting/clustering

Entropy Analysis

Conclusion:



Whole Seizure Main Fr



First 2 sec Seizure Main F

