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Increased Delta-Gamma Phase-Amplitude Coupling and Gamma Bistability during N2 Sleep in Focal Cortical Dysplasia Type 2 Epilepsy

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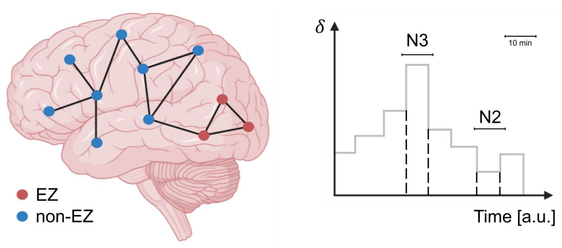
INTRODUCTION

→ Sleep-Related Epilepsy (SRE): Epilepsy subtype marked by seizures during sleep, often linked to focal epilepsy. Focal Cortical Dysplasia (FCD) plays a role in drug-resistant SRE.

→ N2 vs. N3: N2 sees more seizures despite high delta activity in N3[1]. The role of the epileptogenic zone (EZ) in this phenomenon is crucial.

Objective

To identify differences in synchronization, delta-gamma coupling, and bistability patterns between N2 and N3 sleep stages and examine their correlation with epileptic events in patients with FCD2 SRE.



METHODS

Dataset: overnight stereo-electroencephalography (SEEG) recordings spanning seven hours from 14 FCD2 patients. The epileptogenic zone (EZ) was visually identified by clinical experts. We analyzed 10-minute epochs of uninterrupted spontaneous activity of N2 ($n = 135$) and N3 ($n = 62$) sleep.

Metrics: Phase Locking Value (PLV) for the phase synchronization, Phase-Amplitude Coupling (PAC) for the phase-amplitude, and Bistability Index (BiS) for the bistability of neuronal oscillations.

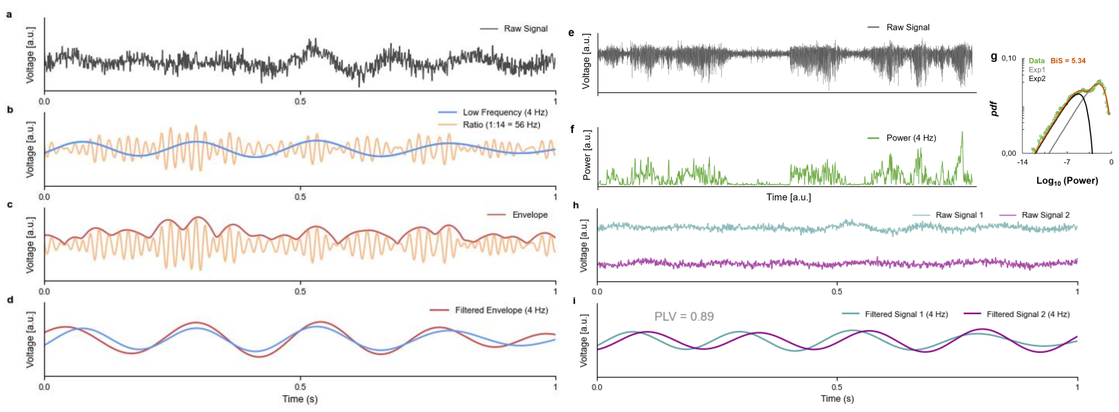


Figure 1: Left Panel – Illustration of Phase-Amplitude Coupling Analysis. **(a)** A synthetic raw neural signal generated for this illustration. **(b)** The signal is filtered with a Morlet wavelet at 4 Hz and 56 Hz (Ratio 1:14). **(c)** The envelope is extracted from the signal filtered at 56 Hz and **(d)** further processed using a Morlet wavelet at a frequency of 4 Hz. PAC is obtained by computing the Phase Locking Value (PLV) between the signals in (d). Top-Right Panel – Illustration of Bistability Analysis[2]. **(e)** Raw signal. **(f)** Power of the signal filtered at 4 Hz. **(g)** Fitting for the BiS index. Bottom-Right Panel – Illustration of PLV Analysis. **(h)** Raw signals. **(i)** Signals filtered at 4 Hz using a Morlet wavelet.

RESULTS

→ Higher values of PLV within the epileptogenic zone, both for N2 and N3.

→ Increase in delta-gamma coupling during N2 sleep when compared to N3 sleep. This difference was particularly prominent within EZ.

→ Higher level of gamma band bistability within the EZ channels when compared to non-EZ channels, both for N2 and N3 sleep.

Phase Synchronization increases within the epileptogenic zone

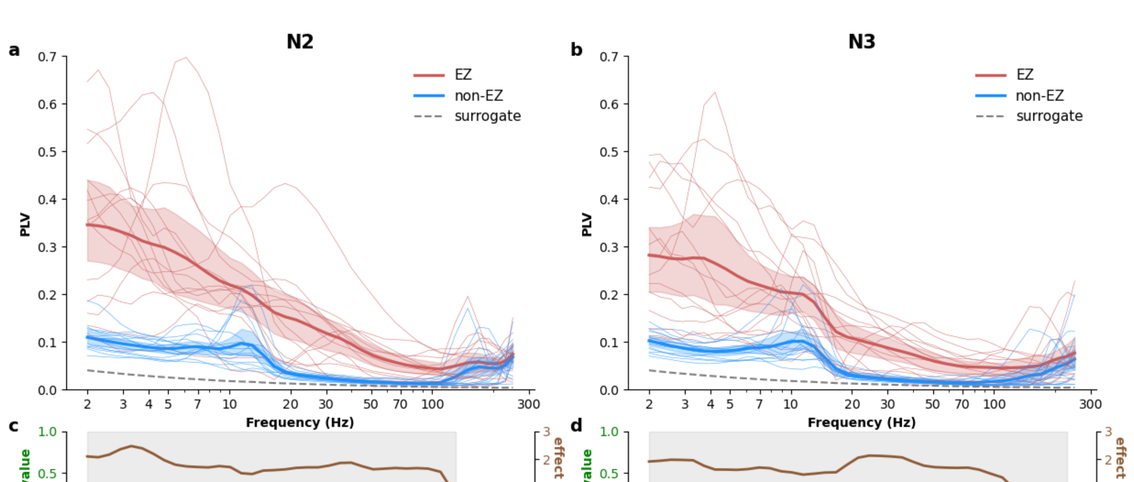


Figure 2: Comparison of Phase Locking Value between EZ and non-EZ channels in both N2 and N3 sleep. **(a)** PLV spectrum for all subjects for N2 and **(b)** N3 sleep. The shaded areas represent the variability computed from 100 bootstraps (95th percentile), while the thin lines correspond to individual subjects. **(c)** p-value (Wilcoxon + FDR Benjamini-Hochberg correction) and effect size (Cohen's d) for the comparison of EZ and non-EZ channels during N2 and **(d)** N3 sleep. The shadow area covers the frequencies in which the p-value is lower than 0.05 and the absolute value of the effect size is higher than 0.3.

Elevated $\delta - \gamma$ Phase-Amplitude Coupling in N2 sleep

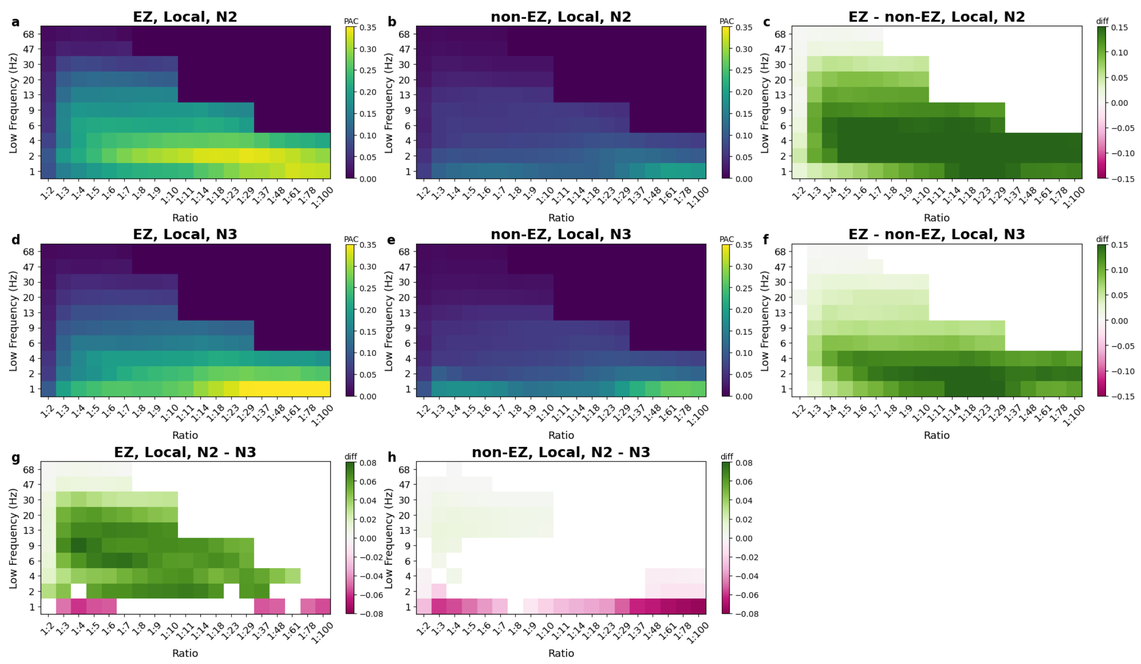


Figure 3: Local PAC Analysis during N2 and N3 Sleep. The heatmaps in the first row represent the local PAC computed for **(a)** the EZ channels and **(b)** non-EZ channels during N2 sleep. Similarly, the second row displays the local PAC results for N3 sleep **(d, e)**. The color intensity in the heatmaps represents the strength of the PAC, with warmer hues indicating higher coupling between phase and amplitude oscillations. The difference between EZ and non-EZ is shown both for **(c)** N2 sleep and **(f)** N3 sleep, whereas the difference between N2 and N3 sleep is shown both within **(g)** EZ channels and **(h)** non-EZ channels. All differences were masked for p-values lower than 0.05 post ranksums testing, with FDR Benjamini-Hochberg correction applied.

Bistability increases in γ band within the epileptogenic zone

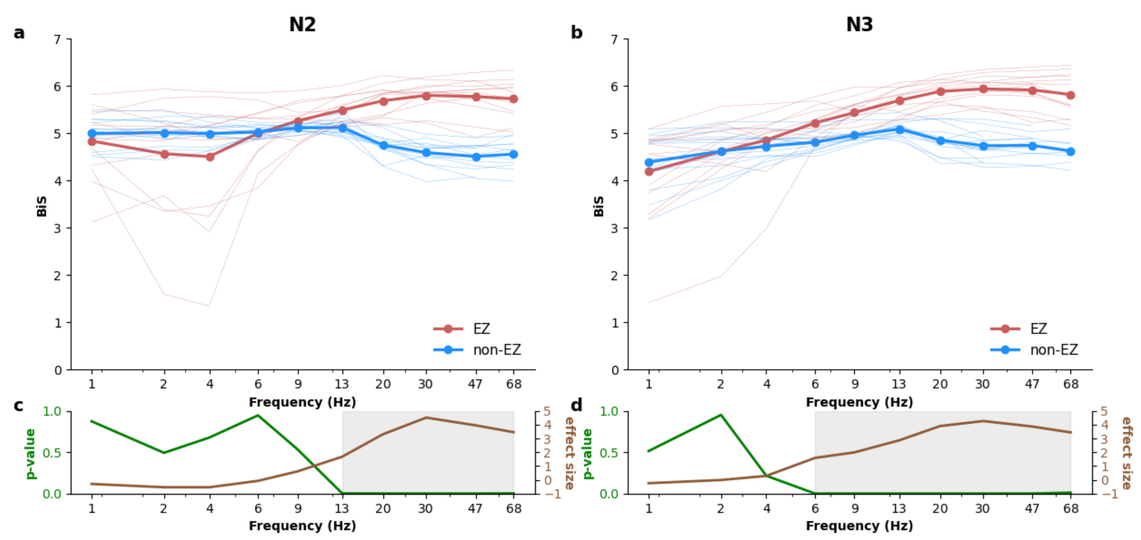


Figure 4: Comparison of bistability index between EZ and non-EZ channels in both N2 and N3 sleep. **(a)** BiS spectrum for all subjects for N2 and **(b)** N3 sleep. The thin lines correspond to individual subjects. **(c)** p-value (Wilcoxon + FDR Benjamini-Hochberg correction) and effect size (Cohen's d) for the comparison of EZ and non-EZ channels during N2 and **(d)** N3 sleep. The shadow area covers the frequencies in which the p-value is lower than 0.05 and the absolute value of the effect size is higher than 0.3.

CONCLUSION

→ Elevated PLV values within the EZ are associated with heightened phase synchronization in that region.

→ The increase of delta-gamma PAC during N2 in EZ suggests stronger synchronization between delta oscillation phase and gamma amplitude, potentially contributing to seizure generation.

→ Higher EZ gamma band bistability in EZ indicates a more pronounced and bistable neural state, likely associated with distinct patterns that contribute to differences in seizure occurrence.

REFERENCES

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[2] S. H. Wang, G. Arnulfo, L. Nobili, et al., "New vistas for epileptogenic zone (EZ) localization and interpretation," bioRxiv, p. 2023.05.21.541570, May 2023. doi: 10.1101/2023.05.21.541570.

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