

Cardiac autonomic dysfunction in pediatric-onset epilepsy: insights from heart rate variability analysis

Giada Vega

IRCCS Fondazione Stella Maris

Vincenzo Russo

University of Campania Luigi Vanvitelli: Università degli Studi della Campania Luigi Vanvitelli

Angelo Comune

University of Campania Luigi Vanvitelli: Università degli Studi della Campania Luigi Vanvitelli

Emanuele Bartolini

`emanuele.bartolini@fsm.unipi.it`

IRCCS Fondazione Stella Maris <https://orcid.org/0000-0002-5683-1941>

Research Article

Keywords: seizures, dysautonomia, children

Posted Date: August 4th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10164870/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Objective

To evaluate the relationship between electroclinical features of epilepsy and cardiac autonomic function, assessed through heart rate variability (HRV), in children and youths with paediatric-onset epilepsies.

Materials and Methods

We prospectively enrolled patients with epilepsy aged 3–25 years who underwent polygraphic EEG recordings, analysing HRV in a 5-minute resting ECG segment. Nine indices were examined, including time-domain, frequency-domain, and nonlinear measures. Associations between HRV parameters and clinical variables were assessed using Spearman correlations and linear regression models adjusted for age and sex. Principal component analysis (PCA) was used to identify composite autonomic profiles.

Results

Ninety-eight patients were included (mean age 14.6 ± 5.2 years; 54.1% female). Earlier epilepsy onset was significantly associated with higher resting heart rate and reduced long-range HRV scaling (lower DFA α_2), suggesting impaired autonomic maturation. The duration of active epilepsy was significantly associated with a composite HRV profile identified by the PCA analysis (PC1; $r = 0.266$, $p = 0.016$), reflecting sympathetic predominance, reduced parasympathetic activity, and altered nonlinear dynamics.

Discussion

Cardiac autonomic regulation appeared to be influenced by the electro-clinical characteristics of epilepsy, mostly dependent on the age at seizure onset and the duration of active epilepsy. The progressive shift toward sympathetic dominance and reduced autonomic complexity warrants to monitor autonomic function in patients with paediatric-onset epilepsies.

KEY BULLET POINTS

Earlier epilepsy onset impairs cardiac autonomic maturation in children

Active epilepsy duration drives progressive sympathovagal dysregulation

PCA reveals a composite autonomic profile linking HRV complexity to epilepsy

INTRODUCTION

Epilepsy is increasingly recognized not only as a disorder of cortical excitability but also as a condition of widespread network dysfunction, also involving the autonomic nervous system. Experimental studies suggest that epileptic activity may propagate beyond the cerebral cortex to engage the Central Autonomic Network (CAN) - a distributed system that includes cortical, limbic, and brainstem structures such as the hippocampus, amygdala, and medullary autonomic centers[1, 2] - with measurable consequences for cardiovascular and respiratory control. Autonomic symptoms are common both ictally

and interictally in vivo, and dysautonomia may contribute to some of the most serious complications of epilepsy, including sudden unexpected death (SUDEP)[3–5]. Yet despite growing recognition of autonomic dysfunction as a clinically meaningful dimension of epilepsy, most evidence comes from adult populations. Paediatric data remain scarce, and the relationship between interictal autonomic function and electroclinical phenotype is poorly characterised in children. Dysautonomia may be explored through a combination of continuous electrodermal activity tracking, multi-lead electrochemical conductance, and cardiorespiratory assessment during EEG-polygraphic recordings[6, 7]. The investigation of heart rate variability (HRV) is particularly well-suited to paediatric populations, providing a sensitive index of sympathovagal modulation and brain–heart axis integrity without requiring active patient cooperation[7].

In this study we aimed to characterise interictal autonomic function in children with epilepsy using HRV analysis derived from ambulatory polygraphic-EEG recordings, and to identify autonomic profiles associated with key electroclinical features.

MATERIALS AND METHODS

We prospectively enrolled consecutive patients with an established diagnosis of epilepsy arising before 18 years of age¹¹, who underwent a polygraphic sleep-deprived EEG recording as part of their routine clinical evaluation (10–20 international system, 256 Hz sampling rate, System Plus, Micromed®, Mogliano Veneto, Italy). Exclusion criteria were concomitant comorbidities or treatments affecting the autonomic nervous system (e.g. diabetes mellitus, metilphenidate).

For each participant, we extracted and analyzed a continuous 5-minute segment devoid of artefacts of the electrocardiographic signal recorded during the resting wakefulness phase. Heart rate variability (HRV) analysis was performed using Kubios HRV® software (version 4.2.0, Kubios Oy, Kuopio, Finland). Artefacts and ectopic beats were corrected using the software's built-in automatic filter.

Statistical analysis

Nine non-redundant HRV outcomes derived from the HRV analysis were pre-specified for all inferential analyses: three time-domain measures (SDNN, RMSSD, and mean HR), three log-transformed frequency-domain measures (VLF, LF, and HF power), the LF/HF ratio, and two nonlinear scaling measures (DFA $\alpha 1$ and DFA $\alpha 2$).

We tested the hypothesis that autonomic parameters could be affected by specific clinical predictors, namely age at epilepsy onset, total epilepsy duration (time intercurrent between age at onset and current age), duration of active epilepsy (time between age at onset and age at last seizure), ongoing seizures (yes vs no), drug resistance (yes vs no), therapy type (monotherapy vs polytherapy vs no therapy), epilepsy type (focal vs generalized vs combined), epilepsy aetiology (genetic vs structural vs undetermined), and brain MRI (normal vs abnormal)

Prior to modelling, multicollinearity among clinical predictors was assessed using an iterative step-down procedure based on the Generalised Variance Inflation Factor ($\text{GVIF}^{1/n-1}$), a generalisation of the standard VIF that accounts for degrees of freedom in categorical predictors. Predictors with $\text{GVIF}^{1/n-1}$ exceeding 2.23 (equivalent to a standard VIF of 5) were to be sequentially removed in a step-down fashion. Age and sex were retained throughout all steps as mandatory covariates.

Descriptive statistics for continuous variables were reported as mean $\pm$ SD with median and range; categorical variables as frequency and percentage. All statistical analyses were performed in R (RStudio version 2024.04.2), using the following packages: *psych* for descriptive statistics, *car* for assumption testing, *effectsize* for effect size estimation, and *ggplot2* for data visualization.

Individual HRV outcome analyses

Bivariate associations between each of the nine HRV indices and the three continuous clinical predictors (age at epilepsy onset, total epilepsy duration, and active epilepsy duration) were assessed using Spearman rank correlations. Adjusted linear regression models were subsequently fitted for each HRV outcome–predictor pair, yielding standardised beta coefficients (β^*) with 95% confidence intervals, controlling for age and sex. For both analyses, multiple comparisons were controlled using the Benjamini-Hochberg false discovery rate (FDR) procedure, applied separately within each clinical predictor (across the nine HRV outcomes per predictor).

Principal component analysis of HRV variables

To reduce the dimensionality of the HRV space and maximise sensitivity when correlating with clinical variables, principal component analysis (PCA) was applied to the nine HRV outcomes. PCA was performed on the standardised (z-scored) correlation matrix so that no variable dominated due to differences in scale or unit. Components were rotated using Varimax orthogonal rotation to maximise interpretability of loadings while preserving the mutual independence of components. Component retention followed the Kaiser criterion (eigenvalue > 1).

Individual component scores were computed for each participant. Associations between PC scores and continuous clinical predictors were assessed with Spearman rank correlations; FDR correction was applied per predictor across the number of retained components. Associations with categorical clinical predictors were assessed using the Kruskal-Wallis test, with η^2 as the effect size measure. These analyses were intended as exploratory and were not subject to multiplicity correction.

Ethics statement

Written informed consent was obtained from all patients and/or their caregivers prior to enrolment. The protocol was approved by the Paediatric Ethics Committee of the Tuscany Region in accordance with the

RESULTS

We evaluated 110 EEG-polygraphic recordings. Twelve exams were discarded for inadequate quality of the electrocardiographic track. We retained 98 patients (54.1% female; mean age 14.6 ± 5.2 years, median 15, range 3–25). Epilepsy onset occurred at a mean age of 6.6 ± 4.8 years (median 6, range 0–21). Mean total epilepsy duration was 8.0 ± 5.4 years (median 7, range 0–20). Mean active epilepsy duration was 6.2 ± 5.3 years (median 5, range 0.3–20) (Table 1).

Table 1
Clinical characteristics of the study population

Epilepsy type	
Generalised	44.9%
Focal	38.8%
Combined	8.2%
DEE (developmental & epileptic encephalopathies)	4.1%
Aetiology	
Unknown	41.8%
Genetic	34.7%
Structural	19.4%
Combined	3.1%
Treatment	
On antiseizure medications (ASMs)	85.7%
<i>Monotherapy</i>	52.0%
<i>Polytherapy</i>	34.7%
Drug-resistant epilepsy	17.3%
Clinical status at assessment	
Ongoing seizures	37.8%
Normal brain MRI	68.4%
Abnormal brain MRI	30.6%

DEE = developmental and epileptic encephalopathies; ASM = antiseizure medication; MRI = magnetic resonance imaging.

HRV parameters

Group-level HRV indices were: SDNN 45.9 ± 22.3 ms (median 42.4), RMSSD 40.4 ± 23.9 ms (median 34.1), and mean HR 86.4 ± 16.5 bpm (median 86.0). Log-transformed spectral power values were: VLF 4.34 ± 0.96 , LF 6.65 ± 0.82 , and HF 6.22 ± 1.21 . The LF/HF ratio was 2.14 ± 1.96 (median 1.81). Nonlinear indices were DFA α_1 1.147 ± 0.252 (median 1.169) and DFA α_2 0.448 ± 0.152 (median 0.436). Full descriptive statistics including absolute spectral power values are reported in Supplementary Table 1.

Preliminary collinearity statistics

After iterative GVIF step-down screening, all the nine clinical predictors were retained in the final model structure, having GVIF^{1/n-1} values between 1.11 and 2.02. Notably, total epilepsy duration and active epilepsy duration, though conceptually related, both met the collinearity threshold (GVIF^{1/n-1} = 2.00 and 2.02, respectively) and were retained as independent predictors.

Individual clinical-autonomic correlations

Two Spearman correlations survived per-predictor FDR correction. Earlier age at epilepsy onset was significantly associated with higher mean HR ($r = -0.309$, $p = 0.002$, FDR-adjusted $p = 0.018$) and lower DFA α_2 ($r = -0.258$, $p = 0.010$, FDR-adjusted $p = 0.047$). Uncorrected positive associations were observed between total epilepsy duration and DFA α_1 ($r = 0.221$, $p = 0.029$) and between active epilepsy duration and DFA α_1 ($r = 0.261$, $p = 0.010$), LF/HF ratio ($r = 0.209$, $p = 0.039$), and DFA α_2 ($r = 0.188$, $p = 0.064$) (Fig. 1, Supplementary Fig. 1, Supplementary Table 2). In age- and sex-adjusted linear regression models, no association reached FDR-corrected significance; however, trends were observed for active epilepsy duration with DFA α_1 ($\beta^* = 0.251$, 95% CI 0.002–0.022, $p = 0.023$), DFA α_2 ($\beta^* = 0.232$, 95% CI 0.000–0.013, $p = 0.035$), and HF power (log) ($\beta^* = -0.229$, 95% CI -0.102 to -0.002, $p = 0.043$), all with FDR-adjusted $p = 0.130$ (Supplementary Table 3).

Principal component analysis

PCA of the nine HRV variables retained two components with eigenvalues exceeding 1.0 (Kaiser criterion), collectively accounting for 71.4% of total HRV variance (PC1: eigenvalue 4.92, 54.6%; PC2: eigenvalue 1.51, 16.7%). Loading patterns after Varimax rotation are detailed in Supplementary Figs. 2–3.

PC1: Sympathovagal balance and nonlinear scaling component (54.6% of variance). PC1 received strong positive loadings from DFA α_1 (0.846), LF/HF ratio (0.840), and DFA α_2 (0.691), and strong negative loadings from HF power (log) (-0.782) and RMSSD (-0.709). Higher PC1 scores therefore reflected elevated sympathovagal ratio alongside higher nonlinear scaling exponents and lower parasympathetic indices, suggesting a sympathetically dominant, autonomically dysregulated profile.

PC2: Overall HRV magnitude and spectral power component (16.7% of variance). PC2 loaded positively on LF power (log) (0.844), VLF power (log) (0.843), SDNN (0.657), RMSSD (0.586), and HF power (log) (0.535), and negatively on mean HR (– 0.642). Higher PC2 scores reflect greater overall HRV magnitude and broader spectral power accompanied by lower resting heart rate.

Clinical correlates of PC scores are illustrated in Fig. 2. Longer active epilepsy duration was the only continuous predictor significantly associated with PC1 after FDR correction ($r = 0.266$, FDR-adjusted $p = 0.016$). PC1 also differed by therapy type ($\eta^2 = 0.047$, $p = 0.039$), though no pairwise comparison survived correction. Patients with combined aetiology had higher PC1 scores than all other aetiological groups (genetic, structural, unknown; all adjusted $p = 0.028$), though this should be interpreted cautiously given the very small group size ($n = 3$). PC1 was also higher in patients with abnormal versus normal MRI ($\eta^2 = 0.043$, $p = 0.049$; adjusted $p = 0.027$).

Patients not receiving antiseizure therapy had higher PC2 scores than those on treatment ($\eta^2 = 0.032$, $p = 0.043$; adjusted $p = 0.043$). All categorical effect sizes were small ($\eta^2 < 0.07$) (Fig. 2). Kruskal-Wallis post-hoc results are hypothesis-generating and were not subject to omnibus FDR correction.

DISCUSSION

Our findings suggest that HRV is modulated by the epilepsy electro-clinical features in patients with pediatric-onset epilepsy. Former studies have demonstrated a reduced interictal HRV in heterogeneous epilepsy populations, such as temporal lobe epilepsy (TLE), genetic and structural drug-resistant epilepsies[3, 4, 8, 9]. This suggests the presence of an impaired vagal modulation and autonomic instability directly attributable to epilepsy. Few studies have been specifically performed in the developmental age. Dhir et al. found a reduction of HRV in children with Dravet syndrome compared to healthy subjects. This autonomic derangement - affecting most time, frequency and non-linear parameters - increased with epilepsy severity and was accompanied by an impaired cerebrovascular blood flow explored by transcranial sonography[10].

Dysautonomia has been found in other paediatric neurogenetic disorders such as Rett syndrome[11], yet the contribution of epilepsy *per se* is still largely unknown.

In our study we first observed that an earlier age at epilepsy onset was independently associated with higher resting heart rate and attenuated long-range fractal scaling of HRV (DFA α_2). This may suggest that the onset of seizures in infancy and early childhood, during which the autonomic system critically develops[12, 13], could have measurable and lasting consequences on cardiac autonomic regulation.

Heart rate at rest is primarily modulated by the balance between cardiac sympathetic and parasympathetic tone; higher mean HR implies reduced vagal tone. The parasympathetic system physiologically matures throughout childhood with a plateau at middle childhood[13–15]. The onset of epilepsy during this critical window may interrupt or delay the developmental trajectory of vagal tone. Indeed, in predisposed subjects dysautonomia appears with short latency after seizure onset, as

demonstrated in adults with temporal lobe epilepsy[9]. Such a precocious derangement could be more intense in children, especially those with a genetic or structural aetiology[10, 16].

The PCA analysis highlighted a complex dysautonomic state in the whole population, mostly explained by PC1 (FDR-adjusted $p = 0.016$) loaded positively by DFA α_1 , LF/HF ratio, DFA α_2 and negatively by HF power, RMSSD. These results correspond to sympathetic dominance and cardiac nonlinear autonomic derangement. The positive loading of short-term detrended fluctuation analysis (DFA α_1 and DFA α_2) hints a degradation of the fractal, healthy irregularities of normal RR-intervals into a highly predictable, rigid structure typically driven by central autonomic stress[14, 17]. Deviations from normal long-range scaling are associated with ageing and cardiovascular disease, reflecting a shift toward less complex and less adaptable physiological dynamics[18, 19]. Concurrently, elevation in the LF/HF ratio suggests a disruption in sympathovagal balance with relative over-activation of sympathetic pathways[20]. The RMSSD quantifies the high-frequency variance of beat-to-beat alterations, its negative loading denotes a loss of immediate vagal modulation as well as HF power [20]. Noteworthy, the dysautonomic balance represented by PC1 was significantly associated to the duration of active epilepsy ($r = 0.266$, FDR-adjusted $p = 0.016$) rather than to the total duration of epilepsy. We may hypothesize that the amount of ongoing epileptic activity, rather than cumulative disease burden alone, drives progressive autonomic dysregulation. This is consistent with animal models demonstrating that repeated seizures produce cumulative ictal and interictal disruption of central autonomic nuclei [21]. The PC1 dysautonomic profile also appeared to be related with therapy type ($\eta^2 = 0.047$, $p = 0.039$) and combined aetiology (combined, genetic, structural, unknown, all adjusted $p = 0.028$) - yet with no significant pairwise comparisons – and with abnormal imaging ($\eta^2 = 0.043$, $p = 0.049$; adjusted $p = 0.027$), as though patients with brain structural alterations were more exposed to dysautonomia. A smaller proportion of HRV variance (16.7%) was captured by PC2, whose higher scores reflected greater overall spectral power and lower resting heart rate, with a significant association with absence of antiseizure therapy ($\eta^2 = 0.032$, adjusted $p = 0.043$). This may be due to the direct pharmacological effects of many ASMs on cardiac autonomic modulation: sodium channel blockers reduce HRV by attenuating sympathetic and parasympathetic efference, while enzyme-inducing agents alter autonomic reflex sensitivity through indirect metabolic pathways[4]. Second, and perhaps more importantly, the direction of confounding is likely to favour untreated patients having intrinsically milder epilepsy and consequently better-preserved autonomic function.

From a cardiological perspective, these findings may be clinically relevant beyond the description of autonomic imbalance. Epilepsy has been associated with a broad spectrum of cardiac rhythm disturbances, including ictal sinus tachycardia, brady-arrhythmias, asystole, atrial arrhythmias, ventricular arrhythmias, and abnormalities of ventricular repolarization. Large-scale data have also suggested that patients with epilepsy carry an increased long-term risk of arrhythmias, supporting the concept that cardiac electrical vulnerability may persist beyond the ictal period[22]. Although most clinically evident rhythm disturbances are seizure-related, chronic autonomic dysfunction, altered central autonomic network activity, antiseizure medications, and, in selected cases, shared or acquired cardio-cerebral channelopathies may contribute to a persistent interictal proarrhythmic substrate[23–25].

Importantly, reduced or dysregulated HRV has been proposed as a non-invasive marker of impaired brain–heart coupling and may be particularly relevant in the framework of the “epileptic heart” and SUDEP pathophysiology[26, 27]. The MORTEMUS study suggested that SUDEP is usually driven by a complex sequence of postictal respiratory dysfunction, central autonomic failure, progressive bradycardia/asystole, and cardiorespiratory arrest, rather than by a single isolated arrhythmic mechanism[28]. Moreover, blunted HRV has been reported in patients who subsequently died of SUDEP, supporting the hypothesis that interictal autonomic impairment may reflect reduced cardiovascular resilience[29]. Therefore, the association observed in our cohort between active epilepsy duration and a composite HRV profile characterized by sympathetic predominance, reduced vagal modulation, and altered nonlinear dynamics should not be interpreted as a direct marker of imminent arrhythmic risk, but rather as an indicator of chronic cardiovascular autonomic burden. This may help identify patients who could benefit from integrated neuro-cardiological assessment, including baseline electrocardiographic evaluation, careful review of antiseizure medications with potential cardiac effects, and prolonged EEG–ECG monitoring in selected cases.

STUDY LIMITATIONS

Several limitations should be acknowledged. The absence of any significant association between drug resistance and HRV may indeed reflect insufficient power to detect effects in the subset of drug-resistant patients. The cross-sectional design precludes causal inference: while the associations between the age at epilepsy onset, the duration of active epilepsy and HRV profiles are consistent with a progressive, seizure-driven autonomic deterioration, alternative explanations (e.g. including reverse causation, shared genetic determinants of epilepsy severity and autonomic function, unmeasured confounders such as seizure frequency, comorbid sleep disorders, or physical activity level) cannot be excluded. Longitudinal studies with serial HRV measurements before and after seizure remission or medication change are needed to establish directionality. Moreover, single-session measurements may not fully capture the dynamic range of autonomic function, and diurnal variation. Finally, the study does not include a healthy paediatric control group, preventing direct quantification of HRV deviation from normative values in this cohort. Future studies should incorporate age- and sex-matched controls to contextualise the absolute magnitude of HRV impairment.

CONCLUSIONS

We found an altered cardiac autonomic regulation in paediatric epilepsy, influenced by the disease course. Earlier seizure onset was associated with higher resting HR and reduced long-range fractal HRV scaling, consistent with a disruption of normal autonomic maturational trajectories. Longer active epilepsy duration pointed to a composite shift toward sympathetic dominance and reduced autonomic complexity, suggesting that seizure activity rather than cumulative disease duration drives progressive autonomic dysregulation. These findings support the routine assessment of HRV as a non-invasive, clinically feasible biomarker of autonomic burden in paediatric epilepsy, and highlight the potential value of achieving early and sustained seizure control in preserving cardiovascular autonomic health.

Declarations

Data availability statement: raw data are available on demand and will be deposited in a public repository

Conflict of interest disclosure: none of the authors has any conflict of interest to disclose

Ethics approval statement: The study was approved by the Paediatrics Ethics Committee of the Tuscany Region, Italy

Patient consent statement: All patients and caregivers have provided consent

Permission to reproduce material from other sources: not applicable

Clinical trial registration: not applicable

ACKNOWLEDGMENT AND FUNDING

This work has been partially supported by the Italian Ministry of Health, grant-RC.

References

1. Bauer J, Devinsky O, Rothermel M, Koch H (2023) Autonomic dysfunction in epilepsy mouse models with implications for SUDEP research. *Front Neurol.* ;13. doi: ARTN 1040648 10.3389/fneur.2022.1040648. PubMed PMID: WOS:000914180300001.
2. Beissner F, Meissner K, Bär KJ, Napadow V (2013) The Autonomic Brain: An Activation Likelihood Estimation Meta-Analysis for Central Processing of Autonomic Function. *J Neurosci* 33(25):10503– PubMed PMID: WOS:000320596400029
3. Sivathamboo S, Constantino TN, Chen Z, Sparks PB, Goldin J, Velakoulis D et al (2020) Cardiorespiratory and autonomic function in epileptic seizures: A video-EEG monitoring study. *Epilepsy Behav* 111:107271. 10.1016/j.yebeh.2020.107271
4. Sivathamboo S, Perucca P (2021) Interictal autonomic dysfunction. *Curr Opin Neurol* 34(2):197–205 doi: 10.1097/WCO.0000000000000906. PubMed PMID: 33664205
5. Christoph B, Stefanie L, Fritz L (2001) Autonomic symptoms during epileptic seizures. *Epileptic Disord* 3(3):103–116
6. Salluce C, Cocciante M, Gazzillo M, Ferrari AR, Battini R, Santorelli FM, Bartolini E (2024) Children and Young Adults with Epilepsy Exhibit an Interictal Autonomic Dysfunction: A Prospective Exploratory Study. *Brain Sci.* ;14(7). Epub 20240629. 10.3390/brainsci14070670. PubMed PMID: 39061411; PubMed Central PMCID: PMCPMC11274926
7. Mason F, Scarabello A, Taruffi L, Pasini E, Calandra-Buonaura G, Vignatelli L, Bisulli F (2024) Heart Rate Variability as a Tool for Seizure Prediction: A Scoping Review. *J Clin Med.* ;13(3). doi: ARTN 747 10.3390/jcm13030747. PubMed PMID: WOS:001160104200001.

8. Frysinger RC, Engel J, Harper RM (1993) Interictal heart rate patterns in partial seizure disorders. *Neurology* 43(10):2136. 10.1212/WNL.43.10.2136
9. Borutta MC, Royle V, Rothballer C, Kraemer F, Gollwitzer S, Hamer H et al (2026) If You Care About Autonomic Modulation-Do Not Let Seizure Seizure. *Diagnostics*. ;16(5). doi: ARTN 698 10.3390/diagnostics16050698. PubMed PMID: WOS:001714575600001
10. Dhir P, Prakash K, Negi S, Maurya AP, Bhatia P, Madaan P et al (2025) Evaluation of autonomic tone and cerebral hemodynamics in children with Dravet syndrome. *Seizure-European J Epilepsy* 131:193–199 PubMed PMID: WOS:001533554500001
11. Rodrigues GD, Cordani R, Veneruso M, Chiarella L, Prato G, Ferri R et al (2024) Predominant cardiac sympathetic modulation during wake and sleep in patients with Rett syndrome. *Sleep Med* 119:188–191 PubMed PMID: WOS:001237194800001
12. Patural H, Pichot V, Flori S, Giraud A, Franco P, Pladys P et al (2019) Autonomic maturation from birth to 2 years: normative values. *Heliyon* 5(3). doi: ARTN e0130010.1016/j.heliyon.2019.e01300. PubMed PMID: WOS:000463067400140
13. Hartevelde LM, Nederend I, ten Harkel ADJ, Schutte NM, de Rooij SR, Vrijkotte TGM et al (2021) Maturation of the Cardiac Autonomic Nervous System Activity in Children and Adolescents. *J Am Heart Assoc*. ;10(4). doi: ARTN e017405 10.1161/JAHA.120.017405. PubMed PMID: WOS:000620612600017.
14. Goldberger AL, Amaral LAN, Hausdorff JM, Ivanov PC, Peng CK, Stanley HE (2002) Fractal dynamics in physiology: Alterations with disease and aging. *P Natl Acad Sci USA* 99:2466–2472. 10.1073/pnas.012579499. PubMed PMID: WOS:000174085900002
15. Pikkujämsä SM, Mäkitallio TH, Sourander LB, Räihä IJ, Puukka P, Skyttä J et al (1999) Cardiac interbeat interval dynamics from childhood to senescence - Comparison of conventional and new measures based on fractals and chaos theory. *Circulation* 100(4):393–399. 10.1161/01.Cir.100.4.393. PubMed PMID: WOS:000081686600014
16. Hödl S, Olbert E, Mahringer C, Carrette E, Meurs A, Gadeyne S et al (2021) Severe autonomic nervous system imbalance in Lennox-Gastaut syndrome patients demonstrated by heart rate variability recordings. *Epilepsy Research*. ;177. doi: ARTN 106783 10.1016/j.eplepsyres.2021.106783. PubMed PMID: WOS:000709740900002
17. Peng CK, Havlin S, Stanley HE, Goldberger AL (1995) Quantification of Scaling Exponents and Crossover Phenomena in Nonstationary Heartbeat Time-Series. *Chaos*. ;5(1):82 – 7. doi: Doi 10.1063/1.166141. PubMed PMID: WOS:A1995RA28200014
18. Shao Z, Hu Z, Tang R, Wang X, Peng W (2026) Daytime dysfunction and SUDEP risk: Exploring the role of sleep and heart rate variability in epilepsy. *Neurología (English Edition)* 41(2):501940. 10.1016/j.nrleng.2026.501940
19. Ryvlin P, Huot M, Valton L, Maillard L, Bartolomei F, Derambure P et al (2026) Seizure-related biomarkers of sudden unexpected death in epilepsy (SUDEP) in drug-resistant focal epilepsy

- (REPO2MSE): a prospective, multicentre case-control study. *Lancet Neurol* 25(1):50–60. 10.1016/S1474-4422(25)00379-5. PubMed PMID: WOS:001641283900001
20. Camm AJ, Malik M, Bigger JT, Breithardt G, Cerutti S, Cohen RJ et al (1996) Heart rate variability - Standards of measurement, physiological interpretation, and clinical use. *Circulation* 93(5):1043–1065 PubMed PMID: WOS:A1996TX43300028
 21. Ravizza T, Balosso S, Vezzani A (2011) Inflammation and prevention of epileptogenesis. *Neurosci Lett* 497(3):223–230. 10.1016/j.neulet.2011.02.040. PubMed PMID: WOS:000292411600011
 22. Xie DY, Liang DD, Zhou LP, Liu Y, Chen YH (2026) Cardiac endogenous transmitter system: molecular features, functions, and clinical implications. *Eur Heart J* 47(2):188–198. 10.1093/eurheartj/ehaf928. PubMed PMID: WOS:001617721600001
 23. Ravindran K, Powell KL, Todaro M, O'Brien TJ (2016) The pathophysiology of cardiac dysfunction in epilepsy. *Epilepsy Res* 127:19–29 PubMed PMID: WOS:000401090200004
 24. Li MCH, O'Brien TJ, Todaro M, Powell KL (2019) Acquired cardiac channelopathies in epilepsy: Evidence, mechanisms, and clinical significance. *Epilepsia* 60(9):1753–1767. 10.1111/epi.16301. PubMed PMID: WOS:000478524700001
 25. Lamberts RJ, Blom MT, Novy J, Belluzzo M, Seldenrijk A, Penninx BW et al (2015) Increased prevalence of ECG markers for sudden cardiac arrest in refractory epilepsy. *J Neurol Neurosurg Ps* 86(3):309–313. 10.1136/jnnp-2014-307772. PubMed PMID: WOS:000349720800013
 26. Manolis TA, Manolis AA, Vouliotis A, Manolis AS (2026) The neuro-cardiac axis in epilepsy. *Eur J Intern Med.* ;146. doi: ARTN 106631 10.1016/j.ejim.2025.106631. PubMed PMID: WOS:001735636900001
 27. Slater JD, Benbadis S, Verrier RL (2024) The brain-heart connection: Value of concurrent ECG and EEG recordings in epilepsy management. *Epilepsy & Behavior Reports.* ;28. doi: ARTN 100726 10.1016/j.ebr.2024.100726. PubMed PMID: WOS:001354962100001
 28. Ryvlin P, Nashef L, Lhatoo SD, Bateman LM, Bird J, Bleasel A et al (2013) Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study. *Lancet Neurol* 12(10):966–977 (13)70214-X. PubMed PMID: WOS:000325905800009
 29. Szurhaj W, Leclancher A, Nica A, Périn B, Derambure P, Convers P et al (2021) Cardiac Autonomic Dysfunction and Risk of Sudden Unexpected Death in Epilepsy. *Neurology* 96(21):E2619–E26. 10.1212/Wnl.00000000000011998. PubMed PMID: WOS:000725294600020

Figures

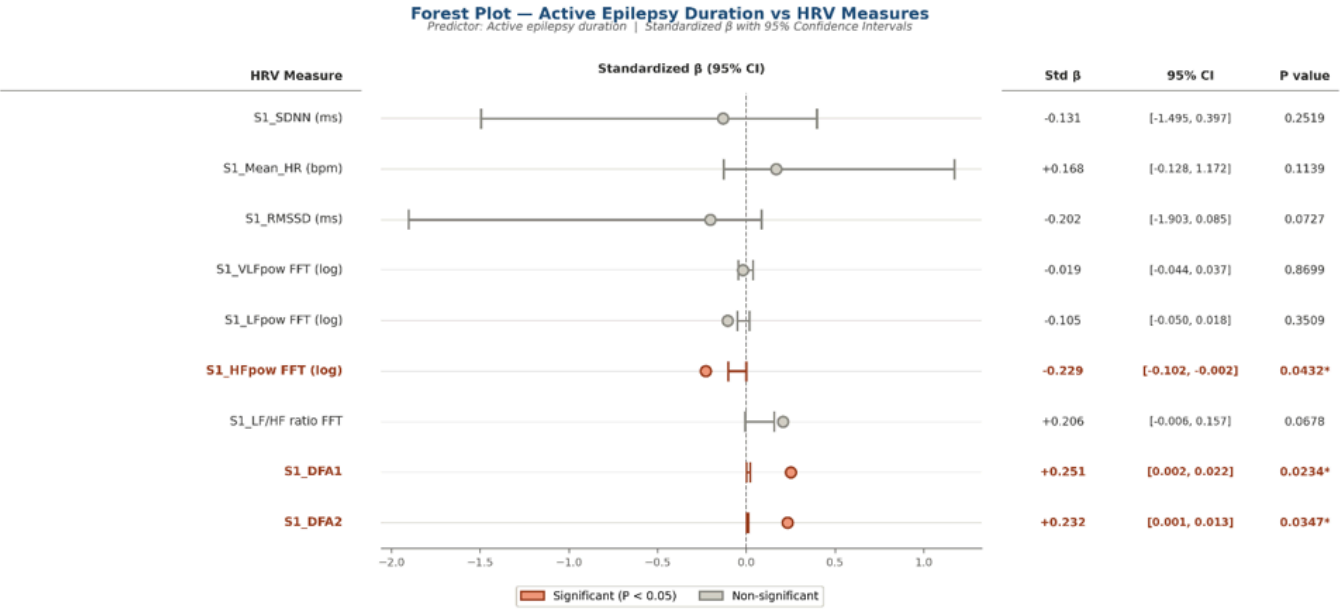


Figure 1

Forest plot showing the correlation between active epilepsy duration and HRV parameters

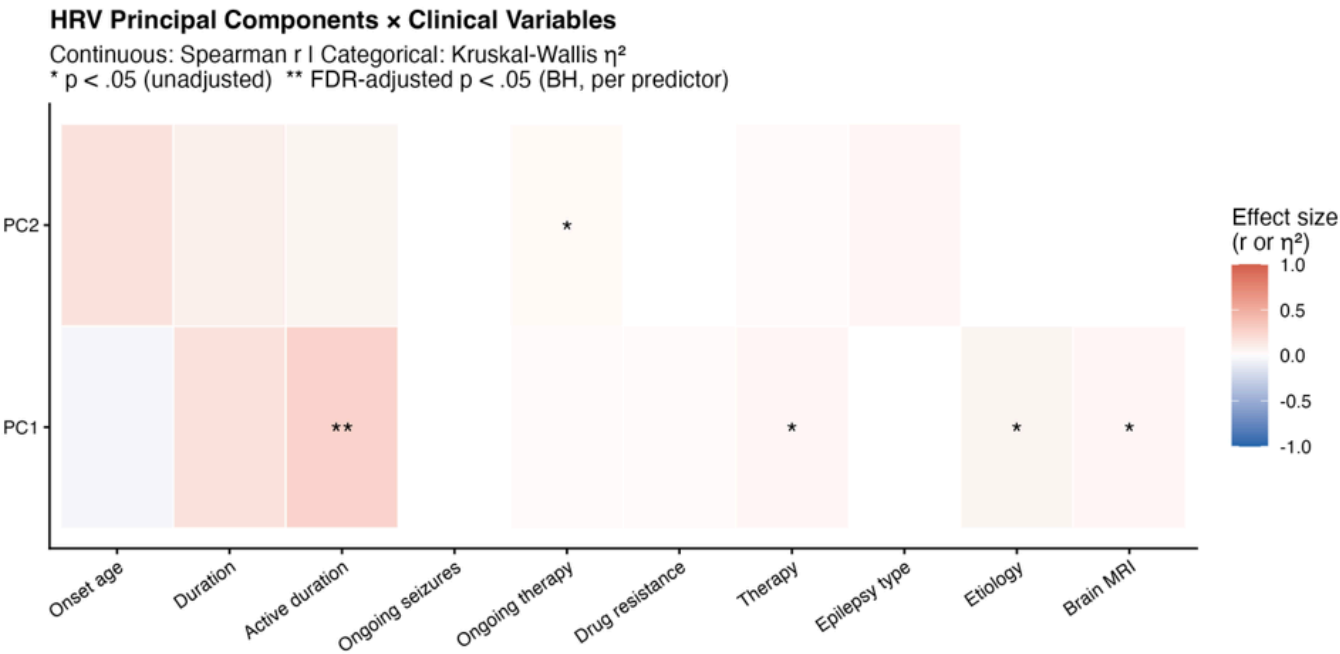


Figure 2

Heatmap depicting the correlation of principal components with clinical variables

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryMaterialHRV11.docx](#)