JNeurosci
THE JOURNAL OF NEUROSCIENCE

Research Articles | Behavioral/Cognitive

Post-Ictal Sleep Changes in Human Focal Epilepsy

https://doi.org/10.1523/JNEUROSCI.0303-25.2026

Received: 12 February 2025
Revised: 30 December 2025
Accepted: 23 January 2026

Post-Ictal Sleep Changes in Human Focal Epilepsy

Vaclav Kremen[1,2,†], Vladimir Sladky[1,2†], Vaclav Gerla [2,†], Yurui Cao[1,3], Filip Mivalt[1], Erik K. St. Louis[1], Mark R. Bower[4], Ben Brinkmann[1], Kai Miller[5], Jamie VanGompel[5], Mark Cook[6], Tim Denison[7], Kent Leyde[8], Gregory A. Worrell[1]

[†]These authors contributed equally to this work.

Author affiliations:

1 Department of Neurology, Mayo Clinic, Rochester, 55905, MN, USA

2 Czech Institute of Informatics, Robotics, and Cybernetics, Czech Technical University in Prague, Prague, 16000, Czech Republic

3 Department of Electrical & Computer Engineering, University of Illinois, Urbana Champaign, IL, USA

4 Department of Neurology, Yale University, New Haven, CT, USA

5 Department of Neurologic Surgery, Mayo Clinic, Rochester, 55905, MN, USA

6 St. Vincent's Hospital and University of Melbourne, Melbourne, Australia

7 Department of Engineering Sciences, Oxford University, Oxford, UK

8 Cadence Neuroscience, Seattle, WA, USA

Correspondence to: Vaclav Kremen and Gregory A. Worrell

Full address 200 First Street SW, Rochester, MN, 55905, USA

E-mail kremen.vaclav@mayo.edu and worrell.gregory@mayo.edu

Abbreviated title: Post-Ictal Sleep Changes in Human

Keywords: Focal epilepsy; Slow wave sleep; Local field potentials; Sleep-wake states; Sleep architecture; Seizure-related consolidation.

Number of pages = 24; Number of figures = 6; Number of tables = 5; Number of multimedia = 0; Number of 3D models = 0; Number of words for abstract = 199; introduction = 649; discussion = 463.

Acknowledgements

This research was supported by the US National Institutes of Health: UH2/UH3-NS95495 and R01-NS09288203. This scientific article is part of the CLARA project that has received funding from the European Union's HORIZON EUROPE research and innovation programme under Grant Agreement No 101136607. The implanted devices were donated by

Medtronic Plc. as part of the National Institutes of Health Brain Initiative. The authors thank the people with epilepsy for participating in this research. We thank Certicon a.s. for the use of CyberPSG tool for the visual review of EEG.

Conflict of interest

G.A.W., V.S., V.K., and B.H.B. declare intellectual property disclosures related to behavioral state and seizure classification algorithms. G.A.W., B.H.B and J.V.G declare intellectual property licensed to Cadence Neuroscience Inc. G.A.W. and J.V.G have licensed intellectual property to NeuroOne, Inc. G.A.W. is an investigator for the Medtronic Deep Brain-Stimulation Therapy for Epilepsy Post-Approval Study. M, C. is chief medical officer at Epiminder Inc., T.D. is co-founder and the Chief Engineer at Amber Therapeutics. K.L is co-founder and the chief executive officer at Cadence Neuroscience, inc. The remaining authors declare that they have no competing interests.

Abstract

Bidirectional interactions between sleep, seizures, and epilepsy remain incompletely understood. Evidence from animal models and people with focal epilepsy suggest that seizures may engage mechanisms of memory consolidation during post-ictal sleep to reinforce and strengthen synaptic connections within the pathological networks that generates seizures, termed seizure-related consolidation (SRC). Human studies of post-ictal sleep changes supportive of SRC, however, are limited by small sample size and restricted observations of post-ictal sleep. We investigated the interplay between seizures and sleep by analyzing sleep-wake and seizure catalogs derived from continuous local field potential (LFP) recordings in 11 people (6 males and 5 females) with drug-resistant focal epilepsy implanted with novel investigational devices and living in their natural environments. Our

findings demonstrate that post-ictal rapid-eye-movement sleep duration is reduced, whereas slow-wave sleep duration, slow-wave LFP spectral power and waveform slope are increased compared to inter-ictal nights without preceding seizures. The most significant changes localize to the epileptogenic networks generating the participants' habitual seizures. These results reveal parallels between SRC and physiological memory consolidation, providing novel insights into the potential role of post-ictal sleep in strengthening epileptic neural engrams, and may have implications for targeted disruption of post-ictal sleep and SRC in focal epilepsy.

Significance Statement

This study uses long-term intracranial local field potential (LFP) recordings to investigate the relationship between seizures and sleep in epilepsy. The post-ictal slow-wave sleep duration, spectral power, and waveform slope are increased compared to inter-ictal. Post-ictal rapid-eye-movement sleep duration is reduced. These changes are most significant within the epileptogenic networks that generate the participants habitual seizures. While this study cannot directly elucidate the mechanism involved in post-ictal sleep modulation, the study results are consistent with post-ictal sleep reinforcing pathological seizure networks through a process similar to physiological memory consolidation, here termed seizure-related consolidation (SRC). These results provide novel insights into the potential role of post-ictal sleep in epilepsy, with implications for potential targeted disruption of post-ictal sleep and SRC.

Introduction

Sleep is essential for brain health and facilitating learning and memory (Huber et al. 2004; Klinzing, Niethard, and Born 2019). Sleep is often disrupted in neurological and psychiatric disorders, but distinguishing whether sleep directly mediates brain dysfunction or simply reflects disease changes remains challenging. Leveraging long-term monitoring in

individuals living in their natural environment has strengthened the connection between poor sleep and chronic medical conditions, underscoring the potential of sleep as a therapeutic target (Zheng et al. 2024).

In epilepsy, the interplay between seizures and sleep has long intrigued clinicians and researchers (Gowers 1885). However, most studies utilizing invasive brain recording are relatively short, multi-day recordings during inpatient hospital settings and inherently limited for investigating the longitudinal interplay between seizures and sleep (Peter-Derex et al. 2020). Growing evidence supports reciprocal sleep-epilepsy relationships, with sleep disturbances increasing seizures (Bazil 2017) and seizures disrupting sleep architecture, including spindles and slow-wave activity (Boly et al. 2017).

Beyond acute seizure events, long-term pathological changes in synaptic connectivity—a hallmark of epileptogenesis—are believed to be a central mechanism in epilepsy progression. In animal models, epileptic activity directly competes with normal plastic changes required for memory formation (Ferrero et al. 2025). Similarly, people with epilepsy often exhibit impaired memory formation that scales proportionally with their overall seizure burden (Hermann et al. 2020). The concept of seizure-related consolidation (SRC) posits that recurrent seizures exploit the mechanisms of memory formation, acting as powerful "engrams" to strengthen pathological networks (Goddard and Douglas 1975; M. Bower et al. 2015; M. R. Bower et al. 2017; M. R. Bower 2024) and alters sleep homeostasis. Evidence of seizure reactivation and consolidation has been observed in individuals with temporal lobe epilepsy (M. R. Bower et al. 2017; M. Bower et al. 2015) supporting parallels between SRC and physiological memory mechanisms. Electrophysiological biomarkers, including inter-ictal epileptiform spikes (IES), high-frequency oscillations, and seizures, may represent powerful, pathological epileptic engrams. These biomarkers are increasingly seen as potential targets

for therapeutic interventions aimed at disrupting SRC processes (Hsu et al. 2008; M. Bower et al. 2015; Ferrero et al. 2025).

While promising, the investigation of SRC and its relationship with sleep in ambulatory humans is hindered by the inaccuracy of self-reported seizure and sleep diaries (Lauderdale et al. 2008; Elger and Hoppe 2018). To address these challenges, we developed machine learning (ML) frameworks for classifying sleep-wake states and detecting seizures from continuous intracranial local field potential (LFP) recordings. The ML algorithms are applied to long-term LFP data from investigational devices implanted in individuals with focal epilepsy and provide accurate sleep-wake and seizure classification catalogs (Kremen et al. 2019; Sladky et al. 2022; Mivalt et al. 2022). We previously used these ML classification algorithms to demonstrate the role of sleep-wake states in multiscale cycles of seizures, IES, mood, impedance, and seizure forecasting (Dell et al. 2021; Mivalt, Kremen, et al. 2023; Kremen et al. 2025).

A particularly interesting finding in our previous studies was that individuals experience longer sleep durations on nights following seizures (Dell et al. 2021). Given sleep's established role in learning and memory (Diekelmann and Born 2010; Walker and Stickgold 2010), this aligns with the hypothesis that post-ictal sleep facilitates the SRC process. Scalp EEG studies are also consistent with this observation, demonstrating increased post-ictal non-REM (NREM) sleep duration, slow-wave activity (SWA), and waveform slope following focal to bilateral tonic-clonic seizures (Boly et al. 2017).

In the current study, chronic intracranial LFP recordings from people with focal epilepsy show increased post-ictal slow-wave sleep duration, SWA spectral power and waveform slope. Interestingly, the post-ictal REM durations are decreased, consistent with previously

reported findings epilepsy monitoring unit studies (Bazil, Castro, and Walczak 2000; Nobili et al. 2025). In summary, the novel long-term LFP data support a possible role for SRC in human epilepsy and highlight the potential of targeting interventions (Ferrero et al. 2025; Lai et al. 2024) to disrupt post-ictal NREM sleep and SRC.

Materials and Methods

Experimental Design and Statistical Analyses

Human Participants

We analyzed two cohorts (cohorts #1 & #2) of human participants with drug-resistant focal epilepsy implanted with investigational devices providing continuous local field potential (LFP) sensing from multiple brain regions (Figure 1A and Figure S1).

Cohort #1 (NC) includes continuous, long-term LFP data from participants implanted with the investigational seizure advisory system (NeuroVista Inc.) between March 24, 2010, and June 21, 2011 in Melbourne, Australia (Cook et al. 2013). Seizure onset networks included neocortical temporal, frontal, and parietal brain regions (Table 1). Participants were implanted with four subdural, 4-contact, cortical strip electrode arrays over the region of the seizure focus. The subdural arrays were connected to lead extensions tunneled down the neck to an implantable subclavicular LFP recording and telemetry unit. The LFP data were wirelessly transmitted to a hand-held device running algorithms to detect and forecast seizures (Cook et al. 2013). Due to various technical factors, the NC cohort suffers from substantial data loss, which potentially limits the scope of our analysis. Consequently, we introduced quantifiable metrics to delineate subjects into inter-ictal and post-ictal groups (Figure 1D): 1.) each participant contributed ≥ 10 days of continuous LF recordings in each period covering both interictal nights (no seizures for at least 48 (NC cohort) or 24h

(mT cohort) before the night) and postictal night (first night within 24h after a seizure) periods. 2.) For each participant, we included only days where ≥ 80 % of the total recording time during the night was successfully recorded. 3.) No missing data either at the beginning or ends of the sleep/nights. Using above criteria, we were able to identify six participants from the NC cohort (5 males and 1 female). We report average data rate in 24-hour day cycle for each NeuroVista participant in Figure S2 in supplementary data (including six selected participants for our study). We show an example of one week data for NC-2 participant with seizures, hypnogram, and electrophysiological features of LFP to demonstrate how sleep scoring reflects power in bands, and the challenge to select interictal data (Figure S3). The opposite scenario can happen with rare seizure occurrence making selection of postictal data challenging. Also note that most of the seizures happen during Awake behavioral state.

Cohort #2 (mT) includes continuous, LFP data from 5 participants (1 male and 4 females) in a clinical trial using the investigational Medtronic Summit RC+S^{TM} between July 10, 2019 and October 23, 2023 at Mayo Clinic, MN, USA (Table S2) (Kremen et al. 2024). All participants had bilateral amygdala-hippocampus onset seizures (Table 1). Four leads with 4-electrode contacts targeted the bilateral amygdala-hippocampus and anterior nucleus of thalamus. Lead extensions were tunneled down the neck to a subclavicular rechargeable, electrical stimulation, LFP sensing, and wireless telemetry device (Figure 1A). The LFP data were wirelessly streamed to a cloud storage using BrainRISE, a platform ecosystem for automatic data capture and automated data analysis (seizure and spike detection, sleep scoring, and participant reporting) (Sladky et al. 2022; Kremen et al. 2025; Mivalt et al. 2022).

The neocortical epilepsy participants (NC 1-6) had electrode contacts in the neocortex targeting seizure onset zone (SOZ) and outside the seizure onset zone (NSOZ). The participants with mT (mT 1-5) had bilateral independent seizures recorded from electrodes in epileptogenic hippocampus bilaterally. Data from these 11 participants was used for the

evaluation of sleep duration, sleep architecture, and slow-wave LFP spectral power and waveform slope. We analyzed SOZ and NSOZ contacts to investigate electrophysiological differences in the brain regions generating seizures in the neocortical epilepsy participants.

All participants from NC and mT cohort provided informed consent for device implantation and research participation, and human subjects research approval was provided by the respective institutional review boards based at University of Melbourne (NC) and Mayo Clinic (mT).

Intracranial Electrophysiology Recordings

The LFP were continuously recorded from multiple brain structures using the NeuroVista and RC+S™ devices (Figure 1). The NeuroVista device recorded 16 channels of subdural LFP data using an average reference (calculated from the 16 contacts) and sampled at 400 Hz (bandwidth 0.85 – 100 Hz) from temporal, frontal, and parietal neocortex. For the NC cohort, we separated electrodes into two groups: Seizure Onset Zone (SOZ) electrodes versus non-SOZ (NSOZ) electrodes. Electrodes were classified based on the seizure onset within a 1-second onset window.

The RC+S™ device recorded four bipolar LFP channels sampled from the 16 parenchyma electrode contacts in the bilateral anterior nucleus of the thalamus (ANT), amygdala (AMG), and hippocampus (HPC). The LFP was sampled at 250 Hz (bandwidth 0.85 – 80 Hz). Long-term recordings from the 5 participants included at least 1 month of LFP data.

The analysis encompassed a combined dataset of **1,501 day-nights** of chronic recordings drawn from both cohorts.

Automated Seizure Detection

We used an automated deep learning model (convolutional neural network with long short-term memory: CNN-LSTM) to label candidate seizures (Sladky et al. 2022). The CNN-LSTM seizure detector was developed and validated previously within a complex study with sensing devices implanted in naturally occurring canine and human epilepsy. Long-term records from humans and canines with epilepsy living in their natural environments provided a large data set of spontaneously occurring seizures. These datasets are highly imbalanced because seizures are relatively rare events when compared to the continuous inter-ictal LFP data. The CNN-LSTM seizure detector represents a technological evolution from early seizure detectors based on hand-crafted features and traditional machine learning to modern methods employing deep learning for automated feature extraction (Nejedly et al. 2019; Sladky et al. 2022). The full performance analysis, including the sensitivity and specificity of the CNN-LSTM seizure detector when applied to this study cohort, is tested by Sladky (Sladky et al. 2022) showing AUROC 0.97+/-0.03 on NC dataset and 0.99+/-0.01 on mT dataset.

In this study the detector's performance, was optimized for high sensitivity and generated a set of candidate seizure detections. These candidate detections were visually reviewed by an epileptologist to accurately identify and annotate true seizures, leveraging the detector's high sensitivity to minimize the risk of missing seizure events.

Automated Behavioral State Classification

We classified sleep-wake states using our previously developed automated machine learning (ML) framework for LFP-based behavioral state classification (Kremen et al. 2019, 2017; Mivalt et al. 2022). This framework in general enables unsupervised, semi-supervised, and supervised learning to classify the behavioral state: Awake, NREM (N2 and N3), and REM(Kremen et al. 2019). The general approach employs a human expert-in-the-loop ML paradigm, training and testing on invasive LFP recordings simultaneous with polysomnography (PSG) scored against AASM criteria (Silber 2012). The validity of the

LFP-based classification against gold-standard scalp PSG has been previously established (Kremen et al. 2019, 2017; Mivalt et al. 2022).

For the medial mT cohort, we utilized the classifier reported previously by Mivalt et al. (Mivalt et al. 2022). The performance metrics for this specific dataset were: overall -score of 0.90 (NREM -score: 0.94; REM -score: 0.67; Awake -score: 0.83), and have been used in prior analyses of the mT cohort (Mivalt et al. 2022; Kremen et al. 2025; Mivalt, Sladky, et al. 2023).

For the NC cohort, we implemented the unsupervised classification framework originally developed and validated on subjects with intracranial electrodes implanted for epilepsy evaluation (Kremen et al. 2019). Given that the NC dataset consisted only of neocortical electrodes (lacking the depth electrodes included in the original validation cohort (Kremen et al. 2019)), we retested the published unsupervised method (Kremen et al. 2019, 2017) to include REM sleep and suitability for transfer to the NC cohort. This retesting involved applying the approach exclusively to data from the neocortical channels of a combined cohort in Kremen at al. (Kremen et al. 2019) (LFP recorded with iEEG using grids and strips only, scalp EEG, and gold-standard PSG annotations), selecting electrode for sleep scoring for each available patient, annotate data based on EEG features, train the classifier, and test/compare the classifier to a gold standard labels. This modified approach yielded an overall accuracy of 0.87 and an estimated F_1 score of 0.82 for Awake, F_1 = 0.87 for REM, and F_1=0.65 for REM, which supports suitability for transfer to the NC data, despite being slightly lower than the original published results that incorporated sEEG electrodes (Kremen et al. 2019, 2017). Final results of the sleep classification for the NC data were used in previous published studies (Dell et al. 2021; Payne et al. 2021).

Electrophysiological Features

The LFP data from subdural strips and penetrating parenchyma electrodes were exported as Multiscale Electrophysiology Format (MEF

https://www.mayo.edu/research/labs/bioelectronics-neurophysiology-engineering/data-code-sharing) files and analyzed using custom algorithms developed in Python programming language (Python 3.8) to characterize LFP features similar to work by Carvalho at el. (Carvalho et al. 2024). Spectral power in all channels was obtained for specific frequency bands of interest in each 30-sec epochs following a previously described approach using Fast Fourier Transform (Kremen et al. 2017), and consistent with previous literature (Varga et al. 2016; Marshall et al. 2006). We first applied a bandpass finite impulse response (FIR) filter with zero-phase-shift to bandpass signal in the 0.5 - 35 Hz band to extract spectral power features. The filter length was 2000, and we used a hamming window design method. A power spectral density related to SWA was calculated in Delta band (1 - 3 Hz). We summarized the data by calculating the mean Delta Power across all visually scored NREM sleep epochs.

We obtained SWA down slopes similar to those of other authors (Riedner et al. 2007; Jaramillo et al. 2020). For artifact-free NREM data segments, we first filter the signal by a bandpass FIR filter with zero phase shift into 0.5 – 35Hz band (same as above). Like Riedner, subsequently, we apply a 50-millisecond moving average filter. Then, we detect zero crossings of the signal and select the descending segments of negative half-waves whose zero crossings were separated by 0.25 to 1.0 seconds for slow waves. We followed the approach similar to Achermann et al. (Bersagliere and Achermann 2010) with filter amplitude set at +/- 5 uV to eliminate waveforms we did not feel confident represented SWA. As discussed by multiple authors in PSG slow wave literature, setting higher amplitude filters is a significant problem in older adult subject due to smaller amplitudes of waveforms, which can lead to bias. Moreover, both Acherman’s and Riedner's studies showed that small or no amplitude cut-off SWs are homeostatically regulated and may be more sensitive than applying amplitude thresholds(Bersagliere and Achermann 2010). Subsequently, we automatically identified troughs of slow waves after each zero-crossing on the signal. And as a final step, we divide the amplitude difference (in μV) (descending negative slope)

by their interval (time difference between them in seconds). Summary slope metrics were obtained by averaging each slow wave slope in delta bands in each 30-second epoch and then across all NREM epochs, generating a mean positive and negative delta-slope estimate during NREM sleep for each electrode (Fig 1D).

We implemented the algorithm and provided examples of its use and documentation in the Behavioral STate Analysis Toolbox (BEST) (https://github.com/bnelair/best-toolbox), a Python package for behavioral state analysis using EEG. BEST includes tools for automated sleep classification of long-term iEEG data recorded using implantable neural stimulation and recording devices, removal of DBS artifacts, and feature extraction from the EEG data, now including delta and slow oscillation slopes. The tools were developed in the Bioelectronics Neurophysiology and Engineering Laboratory at Mayo Clinic, Rochester, MN, USA. The codes for the analysis pipeline above and one specific example of using it one patient and in single night, including the data, can be found at: https://github.com/bnelair/best-toolbox/blob/master/projects/slow_wave_detection/readme.rst

Statistics

We used linear mixed-effects models (LMMs) and generalized linear mixed-effects models (GLMMs) to analyze the effect of seizures on SWA and sleep duration. All statistical analyses were conducted in R programming language. Models were fit using the “lme4” package, with adjusted means and comparisons calculated via the “emmeans” package. LMMs were fitted using restricted maximum likelihood (REML), and degrees of freedom were approximated using the Satterthwaite method. All post-hoc comparisons were adjusted using the Tukey method.

For models with SWA (delta power or delta slope) as the dependent variable, we included a random intercept for each patient-channel interaction to account for repeated measures within subjects and channels. For sleep duration models, which were summarized at the patient level, we included only patient as a random intercept.

Data were categorized using several fixed-effect predictors. These included “channel-type”, defined as SOZ versus NSOZ; “night-type”, defined as “post-ictal” (nights following a seizure) versus “inter-ictal” nights without a preceding seizure; and “night-time”, defined as “Early” (NREM within 2 hours of sleep onset) versus “Late” (NREM more than 4 hours after sleep onset).

For analyzing the effect of post-ictal slowing on sleep length and SWA, we defined immediate post-ictal activity as the 10-minute interval starting 1 minute after seizure offset. The control inter-ictal activity was defined 10-minute intervals starting 3 hours before sleep onset. Separate models were fitted to the NC and mT datasets. We also created a combined dataset model for the sleep duration models.

The analysis of sleep duration involved several LMMs. The sleep duration model included "night-type" as the sole fixed-effect predictor. In a separate model, NREM and REM durations were modeled jointly using the interaction term “night-type” * “sleep-stage” (NREM/REM), which included separate random effects for patient for both NREM and REM.

To analyze the quantitative effect of seizure duration, another LMM for sleep duration used “seizure length” as its sole predictor. Additional LMMs examining the effect of seizure length on SWA power and slope included both “seizure length” and “channel-type” as predictors. Total seizure duration was calculated as the total time in seizure over the 24-hour period preceding (‘ictal day’) the analyzed post-ictal nights. Standardized beta coefficients were calculated for the seizure length estimates from these models.

Changes in SWA (delta power and slope) during post-ictal nights were investigated using a GLMM with a Gamma distribution and log-link function. This model's fixed effects included “channel-type”, “night-type”, and “night-time”, along with two interaction terms: “channel-type” * “night-type” and “night-time” * “night-type”.

Finally, to quantify the relationship between post-ictal power, SWA (delta power and delta slope), we performed a series of linear regressions. These fits were calculated for each

unique patient-channel combination and stratified by “night-type” (inter-ictal vs. post-ictal) and “channel-type” (SOZ vs. NSOZ). The strength of each linear fit was determined by the Pearson's r-value. The resulting distributions of r-values from inter-ictal and post-ictal periods were then compared separately for SOZ and NSOZ channels using a Wilcoxon rank-sum test.

Results

We analyzed two unique long-term LFP datasets from 16 participants with focal drug-resistant mesial temporal lobe epilepsy (mT) and neocortical epilepsy (NC). Our selection criteria, mainly driven by sufficient LFP data rates that allows for the analysis, were fulfilled in 6/11 NC and 5/5 mT participants. A final selection of the 11 patients (5 mT and 6 NC) and their demographics is shown in Table 1. Overall, across all participants, our study analyzed a dataset including 1,501 days with 1,223 days in interictal category and 278 days in postictal category (Table 2).

Table 1 and Table 2 near here.

Figure 1 near here.

Seizures in Ambulatory Participants with Focal Epilepsy

The 11 participants had seizures originating from hippocampus (5/11), temporal neocortex (3/11), frontal neocortex (2/11), or parietal neocortex (1/11) (Table 1). The circadian-ultradian distribution of seizures varied across participants. Seizures were classified into diurnal (daytime: 8AM – 12-midnight), nocturnal (>12midnight – 8AM), or mixed. The participants with mT had mostly diurnal seizures with subject specific unimodal, bimodal or uniform distribution patterns. The participants with neocortical epilepsy have a more varied temporal distribution of seizures occurrence with both nocturnal and diurnal patterns (Figure 2 A&C).

Distribution of Sleep Stages Across Nights in Ambulatory Participants with Focal Epilepsy

The performance of sleep scoring classifier yielded an overall F-1 score of 0.90. Sub-epoch performance was F_1 = 0.94 for REM, F_1 = 0.83 for Awake, and F_1=0.67 for REM sleep. This scoring methodology is consistent with prior analyses of the dataset (Mivalt et al. 2022; Kremen et al. 2025; Mivalt, Sladky, et al. 2023). Lacking gold-standard sleep annotations for the Neocortical (NC) cohort, we adapted our previously validated classification approach. To establish performance relevant to the NC channel locations, we re-trained the classifier exclusively using the neocortical channels from a combined dataset from Kremen et al (Kremen et al. 2019) (LFP recorded with iEEG strips and grids only, scalp EEG, and gold-standard PSG annotations) for each patient and then transferred the approach to the NC dataset. This yielded an overall accuracy of 0.87 and an estimated F_1 score of 0.82 for Awake, F_1 = 0.87 for NREM, and F_1=0.65 for REM, which was deemed acceptable for transfer to the NC data. While this performance was marginally lower than the original published results that incorporated sEEG electrodes (Kremen et al. 2019), the core classification methodology for the NC data aligns with our prior work (Kremen et al. 2019; Mivalt et al. 2022; Mivalt, Sladky, et al. 2023). The same results for NC sleep classification (sleep labels) were previously used in studies analyzing the NeuroVista data (Dell et al. 2021; Payne et al. 2021).

The circular histograms of the diurnal distribution of behavioral states (Wakefulness, NREM, REM) and seizures reveal participant-specific seizure and sleep patterns (Figure 2). Except for participants mT-2 & NC-3 who had very little REM, the circular histograms for sleep-wake show increased NREM compared to REM in the early part of the night followed by shift to more NREM/REM cycles with longer REM sleep duration later in the night, as was reported in limited duration sleep-wake studies (Merica and Gaillard 1986; Fuller, Gooley, and Saper 2006). Three participants with mT had markedly reduced REM/NREM ratios (mT-2, NC-3,

NC-5). The remaining participants had more physiologically normal sleep distributions, with more NREM sleep early in the night and more REM sleep later in the night sleep cycle.

Figure 2 near here.

Seizure-associated alterations in sleep architecture and electrophysiology

Analysis of sleep duration (Figure 3, Table 3, Table S1) shows the alternation of total sleep duration and NREM sleep in post-ictal versus inter-ictal sleep. Both average total sleep time (TST) and average NREM sleep time across participants were longer during nights following daytime seizures (post-ictal nights) than for interictal nights. Average postictal night TST was 8.83 ± 0.30 hours vs. interictal night TST of 8.43 ± 0.29 hours ($p<0.01$), while post-ictal night average NREM sleep time was 6.03 ± 0.29 hours vs. interictal night NREM sleep time of 5.69 ± 0.29 hours ($p <0.001$). On the contrary the REM phase of sleep was shortened, with 1.47 ± 0.21 hours post-ictal vs. 1.67 ± 0.20 in interictal nights ($p<0.05$, Table 3).

Figure 3 and Table 3 near here.

There were also post-ictal sleep changes on microarchitectural and electrophysiological levels. Both SWA (1 – 3 Hz power and LFP waveform slope) during NREM sleep were increased on post-ictal nights compared to inter-ictal nights (Figure 4, Table 4). The delta LFP power was higher in post-ictal sleep in both cohorts in early and late phases of the night, but larger in the early night (Table 4). Furthermore, the increased SWA (both power and slope) were greater in the SOZ compared to NSOZ in the neocortical participants where the analysis was possible (Table 4). The increased delta power was greater during the early portion of the night (first two hours of the night) but also persisted into the latter half of the night (more than 4 hours into the night) in both SOZ and NSOZ electrodes. Similar results appeared in the mT cohort during the early night, involving only the SOZ electrodes,

where SWA (both delta power and slope) were higher in the early part of post-ictal nights. Notably, we found similar findings of larger post-ictal effects on SWA early in the night compared to later in the sleep cycle, consistent with previous observations from shorter data sets by Boly et al. (Boly et al. 2017).

Figure 4 and Table 4 near here.

We also investigated if there were any effects of seizure length (distributions of seizure durations for each patient is shown in supplementary data in Figure S4) or electrophysiological post-ictal slowing on electrophysiology dynamics of SWA and sleep structure at nights after seizures. Our results suggest that seizure duration calculated as a sum of the durations of all seizures occurring during the ictal day preceding the analyzed post-ictal night does not significantly affect total sleep, NREM, or REM duration and has minimal impact on SWA (both delta power and slope) in early phase of post-ictal nights (Figure 5 and Table 5). To test the effect of post-ictal slowing on SWA in post-ictal nights, we characterized post-ictal slowing as a post-ictal delta power and tested its effect on SWA electrophysiological markers (delta power and slope). We found that post-ictal delta power is less correlated with SWA (delta power and slope) than during control interictal days. The median r-value = 0.26 for delta power in post-ictal nights while in inter-ictal night median r-value = 0.56 ($p < 0.01$). Similarly for delta slope median r-value in post-ictal nights is 0.24 compared to 0.49 in inter-ictal nights ($p<0.001$). This was only true in pathological regions of the brain in SOZ electrodes while there was no effect found in NSOZ electrodes (Figure 6).

Figure 5 and 6 near here.

Discussion

This study investigated post-ictal slow wave sleep using long-term continuous LFP recordings in ambulatory participants with focal epilepsy living in their natural home environment. We quantified inter-ictal and post-ictal slow-wave sleep and observed

consistent changes in post-ictal slow wave sleep duration, SWA spectral power, and SWA slope. While increased NREM sleep duration may simply reflect the brain's restorative process following the physiological stress of a seizure, our electrophysiological findings are consistent with studies of systems-related consolidation with enhanced slow-wave activity as a key biomarker (Klinzing, Niethard, and Born 2019). Similar findings were also reported in short-term scalp EEG studies where sleep SWA power and waveform slope were positively correlated with the frequency of secondary generalized seizures in the days preceding sleep and at scalp locations associated with the underlying focal epilepsy localization (Boly et al. 2017; Moffet et al. 2020). Focal increases in sleep SWA in the nights after motor learning tasks have also been described in neurologically normal research participants (Huber et al. 2004). In summary, the findings presented here support a process of seizure-related consolidation in human focal epilepsy. While prior studies of systems-related consolidation have largely focused on NREM sleep, and where we report consistent electrophysiology features, the exploration of post-ictal REM sleep changes is relevant for a complete picture of memory and emotional regulation. Here we found that overall REM sleep duration is decreased in the nights after seizures. This is consistent with previously reported findings in short-term studies at Epilepsy Monitoring Units (Bazil, Castro, and Walczak 2000; Nobili et al. 2025). Future investigations will focus more broadly on focal epilepsy sleep architecture.

Furthermore, animal models support targeting consolidation to disrupt seizure related consolidation in epileptic networks (Lai et al. 2024; Ferrero et al. 2025). Lai et al. recently showed that a mammalian target of rapamycin (mTOR) signaling pathway inhibitor delivered during the post-ictal period yielded the largest seizure and IES reduction, and subsequently demonstrated similar findings for IES in a pilot human trial. While Ferrero at el. showed how properly spatiotemporally targeted closed-loop electrical brain stimulation can eliminate the abnormal cortical activity patterns and prevent progression of long-term spatial memory

deficits in rodents with epilepsy. These studies suggest the potential importance of post-ictal targeting of interventions to prevent or reduce pathologic consolidation of epilepsy engrams.

Studies in larger numbers of participants are required to confirm the preliminary findings reported here. Future studies should also address the relationships between sleep patterns and common comorbidities, such as memory, mood and cognitive dysfunction. Lastly, these findings may prove useful for investigating targeted neuromodulation using currently available brain stimulation devices to disrupt consolidation of seizure engrams during post-ictal slow wave sleep. We have recently initiated such a trial in people with focal epilepsy implanted with anterior nucleus of thalamus FDA approved devices.

Data and Software Availability

The data underlying this article will be shared upon reasonable request to the corresponding authors. The software tools created by authors and used for this article are published at Mayo Clinic's Bioelectronics Neurophysiology and Engineering Laboratory webpage (https://www.mayo.edu/research/labs/bioelectronics-neurophysiology-engineering/overview) and Github repository (https://github.com/bnelair).

References

Bazil, Carl W. 2017. “Sleep and Epilepsy.” *Seminars in Neurology* 37 (4): 407–12.

Bazil, Carl W., Luiz H. M. Castro, and Thaddeus S. Walczak. 2000. “Reduction of Rapid Eye Movement Sleep by Diurnal and Nocturnal Seizures in Temporal Lobe Epilepsy.” *Archives of Neurology* 57 (3): 363.

Bersagliere, Alessia, and Peter Achermann. 2010. “Slow Oscillations in Human Non-Rapid Eye Movement Sleep Electroencephalogram: Effects of Increased Sleep Pressure.” *Journal of Sleep Research* 19 (1 Pt 2): 228–37.

Boly, Melanie, Benjamin Jones, Graham Findlay, Erin Plumley, Armand Mensen, Bruce Hermann, Guilio Tononi, and Rama Maganti. 2017. “Altered Sleep Homeostasis Correlates with Cognitive Impairment in Patients with Focal Epilepsy.” *Brain: A Journal of Neurology*. https://doi.org/10.1093/brain/awx017.

Bower, Mark R. 2024. “Review: Seizure-Related Consolidation and the Network Theory of Epilepsy.” *Frontiers in Network Physiology* 4 (August): 1430934.

Bower, Mark R., Michal T. Kucewicz, Erik K. St. Louis, Fredric B. Meyer, W. Richard Marsh, Matt Stead, and Gregory A. Worrell. 2017. “Reactivation of Seizure-Related Changes to Interictal Spike Shape and Synchrony during Postseizure Sleep in Patients.” *Epilepsia* 58 (1): 94–104.

Bower, Mark, M. Stead, R. S. Bower, M. T. Kucewicz, V. Sulc, J. Cimbalnik, B. H. Brinkmann, et al. 2015. “Evidence for Consolidation of Neuronal Assemblies after Seizures in Humans.” *Journal of Neuroscience* 35 (3). https://doi.org/10.1523/JNEUROSCI.3019-14.2015.

Carvalho, Diego Z., Vaclav Kremen, Filip Mivalt, Erik K. St Louis, Stuart J. McCarter, Jan Bukartyk, Scott A. Przybelski, et al. 2024. “Non-Rapid Eye Movement Sleep Slow-Wave Activity Features Are Associated with Amyloid Accumulation in Older Adults with Obstructive Sleep Apnoea.” *Brain Communications* 6 (5): fcae354.

Cook, Mark J., Terence J. O’Brien, Samuel F. Berkovic, Michael Murphy, Andrew Morokoff, Gavin Fabinyi, Wendyl D’Souza, et al. 2013. “Prediction of Seizure Likelihood with a Long-Term, Implanted Seizure Advisory System in Patients with Drug-Resistant Epilepsy: A First-in-Man Study.” *Lancet Neurology* 12 (6): 563–71.

Dell, Katrina L., Daniel E. Payne, Vaclav Kremen, Matias I. Maturana, Vaclav Gerla, Petr Nejedly, Gregory A. Worrell, et al. 2021. “Seizure Likelihood Varies with Day-to-Day Variations in Sleep Duration in Patients with Refractory Focal Epilepsy: A Longitudinal Electroencephalography Investigation.” *EClinicalMedicine* 37 (July). https://doi.org/10.1016/j.eclinm.2021.100934.

Diekelmann, Susanne, and Jan Born. 2010. “The Memory Function of Sleep.” *Nature Reviews. Neuroscience* 11 (2): 114–26.

Elger, Christian E., and Christian Hoppe. 2018. “Diagnostic Challenges in Epilepsy: Seizure under-Reporting and Seizure Detection.” *Lancet Neurology* 17 (3): 279–88.

Ferrero, Jose J., Ahnaf R. Hassan, Zelin Yu, Zifang Zhao, Liang Ma, Cynthia Wu, Shan Shao, et al. 2025. “Closed-Loop Electrical Stimulation Prevents Focal Epilepsy Progression and Long-Term Memory Impairment.” *Nature Neuroscience* 28 (8): 1753–62.

Fuller, Patrick M., Joshua J. Gooley, and Clifford B. Saper. 2006. “Neurobiology of the Sleep-Wake Cycle: Sleep Architecture, Circadian Regulation, and Regulatory Feedback.” *Journal of Biological Rhythms* 21 (6): 482–93.

Goddard, G. V., and R. M. Douglas. 1975. “Does the Engram of Kindling Model the Engram of Normal Long Term Memory?” *The Canadian Journal of Neurological Sciences. Le Journal Canadien Des Sciences Neurologiques* 2 (4): 385–94.

Gowers, W. R. 1885. “Recent Literature Lectures on the Diagnosis of Diseases of the Brain, Delivered at University College Hospital.” *The Boston Medical and Surgical Journal* 113 (26): 624–25.

Hermann, Bruce, Lisa L. Conant, Cole J. Cook, Gyujoon Hwang, Camille Garcia-Ramos, Kevin Dabbs, Veena A. Nair, et al. 2020. “Network, Clinical and Sociodemographic Features of Cognitive Phenotypes in Temporal Lobe Epilepsy.” *NeuroImage. Clinical* 27 (102341): 102341.

Hsu, David, Wei Chen, Murielle Hsu, and John M. Beggs. 2008. “An Open Hypothesis: Is Epilepsy Learned, and Can It Be Unlearned?” *Epilepsy and Behavior*. https://doi.org/10.1016/j.yebeh.2008.05.007.

Huber, Reto, M. Felice Ghilardi, Marcello Massimini, and Giulio Tononi. 2004. “Local Sleep and Learning.” *Nature*. https://doi.org/10.1038/nature02663.

Jaramillo, V., C. Volk, A. Maric, M. Furrer, S. Fattinger, S. Kurth, C. Lustenberger, and R. Huber. 2020. “Characterization of Overnight Slow-Wave Slope Changes across Development in an Age-, Amplitude-, and Region-Dependent Manner.” *Sleep* 43 (9). https://doi.org/10.1093/sleep/zsaa038.

Klinzing, Jens G., Niels Niethard, and Jan Born. 2019. “Mechanisms of Systems Memory Consolidation during Sleep.” *Nature Neuroscience* 22 (10): 1598–1610.

Kremen, B. H. Brinkmann, J. J. Van Gompel, M. Stead, E. K. St Louis, and G. A. Worrell. 2019. “Automated Unsupervised Behavioral State Classification Using Intracranial Electrophysiology.” *Journal of Neural Engineering* 16 (2). https://doi.org/10.1088/1741-2552/aae5ab.

Kremen, J. J. Duque, B. H. Brinkmann, B. M. Berry, M. T. Kucewicz, F. Khadjevand, J. Van Gompel, M. Stead, E. K. St Louis, and G. A. Worrell. 2017. “Behavioral State Classification in Epileptic Brain Using Intracranial Electrophysiology.” *Journal of Neural Engineering* 14 (2). https://doi.org/10.1088/1741-2552/aa5688.

Kremen, Vaclav, Vladimir Sladky, Filip Mivalt, Nicholas M. Gregg, Irena M. Balzekas, Tory Marks, Benjamin Henry Brinkmann, et al. 2024. “Platform for Brain Network Sensing and Stimulation with Quantitative Behavioral Tracking: Application to Limbic Circuit Epilepsy.” medRxiv. https://doi.org/10.1101/2024.02.09.24302358.

Kremen, Vaclav, Vladimir Sladky, Filip Mivalt, Nicholas M. Gregg, Benjamin H. Brinkmann, Irena Balzekas, Victoria Marks, et al. 2025. “Modulating Limbic Circuits in Temporal Lobe Epilepsy: Impacts on Seizures, Memory, Mood and Sleep.” *Brain Communications* 7 (2): fcaf106.

Lai, Shirong, Libo Zhang, Xinyu Tu, Xinyue Ma, Yujing Song, Kexin Cao, Miaomiao Li, et al. 2024. “Termination of Convulsion Seizures by Destabilizing and Perturbing Seizure Memory Engrams.” *Science Advances* 10 (12): eadk9484.

Lauderdale, Diane S., Kristen L. Knutson, Lijing L. Yan, Kiang Liu, and Paul J. Rathouz. 2008. “Self-Reported and Measured Sleep Duration: How Similar Are They?” *Epidemiology (Cambridge, Mass.)* 19 (6): 838–45.

569 Marshall, Lisa, Halla Helgadóttir, Matthias Mölle, and Jan Born. 2006. “Boosting Slow
570 Oscillations during Sleep Potentiates Memory.” *Nature* 444 (7119): 610–13.

571 Merica, H., and J-M Gaillard. 1986. “Internal Structure of Sleep Cycles in a Healthy
572 Population.” *Sleep* 9 (4): 502–13.

573 Mivalt, Filip, Vaclav Kremen, Vladimir Sladky, Irena Balzekas, Petr Nejedly, Nicholas M.
574 Gregg, Brian Nils Lundstrom, et al. 2022. “Electrical Brain Stimulation and
575 Continuous Behavioral State Tracking in Ambulatory Humans.” *Journal of Neural*
576 *Engineering* 19 (1): 016019.

577 Mivalt, Filip, Vaclav Kremen, Vladimir Sladky, Jie Cui, Nicholas M. Gregg, Irena Balzekas,
578 Victoria Marks, et al. 2023. “Impedance Rhythms in Human Limbic System.” *Journal*
579 *of Neuroscience* 43 (39): 6653–66.

580 Mivalt, Filip, Vladimir Sladky, Samuel Worrell, Nicholas M. Gregg, Irena Balzekas, Inyong
581 Kim, Su-Youne Chang, et al. 2023. “Automated Sleep Classification with Chronic
582 Neural Implants in Freely Behaving Canines.” *Journal of Neural Engineering* 20 (4):
583 046025.

584 Moffet, Eric W., Ruben Verhagen, Benjamin Jones, Graham Findlay, Elsa Juan, Tom
585 Bugnon, Armand Mensen, et al. 2020. “Local Sleep Slow-Wave Activity Colocalizes
586 With the Ictal Symptomatogenic Zone in a Patient With Reflex Epilepsy: A High-
587 Density EEG Study.” *Frontiers in Systems Neuroscience*.
588 https://doi.org/10.3389/fnsys.2020.549309.

589 Nejedly, Petr, Vaclav Kremen, Vladimir Sladky, Mona Nasseri, Hari Guragain, Petr Klimes,
590 Jan Cimbalnik, Yogatheesan Varatharajah, Benjamin H. Brinkmann, and Gregory A.
591 Worrell. 2019. “Deep-Learning for Seizure Forecasting in Canines with Epilepsy.”
592 *Journal of Neural Engineering* 16 (3): 036031.

593 Nobili, Lino, Ramona Cordani, Dario Arnaldi, Pietro Mattioli, Marco Veneruso, and Marcus
594 Ng. 2025. “Rapid Eye Movement Sleep and Epilepsy: Exploring Interactions and
595 Therapeutic Prospects.” *Journal of Sleep Research* 34 (2): e14251.

596 Payne, Daniel E., Katrina L. Dell, Phillipa J. Karoly, Vaclav Kremen, Vaclav Gerla, Levin
597 Kuhlmann, Gregory A. Worrell, Mark J. Cook, David B. Grayden, and Dean R.
598 Freestone. 2021. “Identifying Seizure Risk Factors: A Comparison of Sleep, Weather,
599 and Temporal Features Using a Bayesian Forecast.” *Epilepsia* 62 (2): 371–82.

600 Peter-Derex, Laure, Petr Klimes, Véronique Latreille, Sarah Bouhadoun, François Dubeau,
601 and Birgit Frauscher. 2020. “Sleep Disruption in Epilepsy: Ictal and Interictal Epileptic
602 Activity Matter.” *Annals of Neurology* 88 (5): 907–20.

603 Riedner, Brady a., Vladyslav V. Vyazovskiy, Reto Huber, Marcello Massimini, Steve Esser,
604 Michael Murphy, and Giulio Tononi. 2007. “Sleep Homeostasis and Cortical
605 Synchronization: III. A High-Density EEG Study of Sleep Slow Waves in Humans.”
606 *Sleep* 30 (12): 1643–57.

607 Silber, Michael H. 2012. “Staging Sleep.” *Sleep Medicine Clinics* 7 (3): 487–96.

608 Sladky, Vladimir, Petr Nejedly, Filip Mivalt, Benjamin H. Brinkmann, Inyong Kim, Erik K. St.
609 Louis, Nicholas M. Gregg, et al. 2022. “Distributed Brain Co-Processor for Tracking

610 Spikes, Seizures and Behaviour during Electrical Brain Stimulation." *Brain*
611 *Communications* 4 (3): fcac115.

612 Varga, Andrew W., Margaret E. Wohlleber, Sandra Giménez, Sergio Romero, Joan F.
613 Alonso, Emma L. Ducca, Korey Kam, et al. 2016. "Reduced Slow-Wave Sleep Is
614 Associated with High Cerebrospinal Fluid Aβ42 Levels in Cognitively Normal Elderly."
615 *Sleep* 39 (11): 2041–48.

616 Walker, Matthew P., and Robert Stickgold. 2010. "Overnight Alchemy: Sleep-Dependent
617 Memory Evolution." *Nature Reviews. Neuroscience*. Springer Science and Business
618 Media LLC.

619 Zheng, Neil S., Jeffrey Annis, Hiral Master, Lide Han, Karla Gleichauf, Jack H. Ching,
620 Melody Nasser, et al. 2024. "Sleep Patterns and Risk of Chronic Disease as
621 Measured by Long-Term Monitoring with Commercial Wearable Devices in the All of
622 Us Research Program." *Nature Medicine* 30 (9): 2648–56.

623

Figure legends

Figure 1. Continuous long-term monitoring of local field potentials (LFP) in people with drug resistant focal epilepsy. (**A**) Investigational implantable neural sensing devices were used to record continuous long-term LFP from amygdala-hippocampus in 5 participants with mesial temporal lobe epilepsy (mT) and in 6 participants with frontal, temporal or parietal neocortical epilepsy. (**B**) Validated automated machine learning algorithms were used to detect electrographic seizures and to classify each 10 second window of continuous LFP as inter-ictal (non-seizure) or ictal (seizure). (**C**) Sleep-wake state was classified as wakefulness (W), rapid eye movement (REM) or REM (N1, N2, or N3) sleep. (**D**) The data were split into nights after seizures (post-ictal) and nights without prior seizures in last 48-hours (inter-ictal). The duration of wakefulness, NREM, and REM and slow-wave sleep activity LFP micro-sleep features were analyzed.

Figure 2. Circadian distributions of seizures and sleep-wake using continuous long-term local field potentials (LFP). The LFP recorded from participants with mesial temporal epilepsy (mT) or neocortical focal epilepsy (NC) over months. (**A**) 5 participants with mT (mT 1-5) and seizures recorded from amygdala-hippocampus. Seizures were diurnal with seizures occurring at participant specific time-of-day. (**B**) Participants with focal neocortical seizures recorded from temporal (NC 1-3), frontal (NC 4-5) and parietal (NC-6) localizations. One participant had nocturnal seizures (NC-3) with decreased REM during the night (**C&D**) Circular histograms of sleep-wake states for mT and NC participants (frontal, temporal and parietal).

Figure 3. Macro-architecture of inter-ictal and post-ictal sleep. Total sleep duration is the is the elapsed time from sleep onset to sleep offset. NREM sleep duration is the sum of all NREM sleep stages. Total sleep time duration as well as NREM duration was increased for post-ictal versus inter-ictal slow-wave sleep. REM sleep duration, however was shorter on nights after seizures compared to inter-ictal nights. Individual subject mean values ± standard deviation in gray. The Black lines represent estimated fixed effects of a Linear Mixed Effect Model (* $p < 0.05$, ** $p < 0.01$, **** $p < 0.0001$) with error bars showing 95% confidence intervals.

Figure 4. Micro-architecture of sleep in post-ictal nights. Analysis of Local field potentials (LFP) in slow-wave (NREM) sleep in inter-ictal nights and post-ictal nights after seizures. Inter-ictal night was defined by absence of seizures during the preceding **24** hours. Post-ictal night was defined as sleep after seizures during awake time preceding the night. The LFP slow-wave analysis during NREM sleep was performed to quantify the slow-wave slope (**Top**) and delta frequency (1 - 3 Hz) band power (**Bottom**). The LFP slow-wave slope was increased during post-ictal nights compared to inter-ictal nights for both mT and NC participants. The LFP delta power was increased during post-ictal nights compared to inter-ictal nights for mT and NC participants. Same trend is visible in both seizure onset zone (SOZ) and non-seizure onset zone (NSOZ) electrodes. For both, delta band power and delta slope the absolute values are higher at SOZ versus NSOZ electrodes. In NC cohort, SOZ electrodes have a positive significant interaction in postictal nights for Delta power ($p<0.05$), and Delta slope ($p<0.01$). The results show Estimated Marginal Means (EMMs) contrasts from the output of Generalized Linear Mixed Effect Model. Error bars represent 95% confidence intervals. P-values were adjusted for multiple comparisons using the Tukey method. (* $p < 0.05$, **** $p < 0.0001$).

Figure 5. Effect of seizure length on electrophysiological biomarkers in post-ictal nights. The figure shows distribution of a logarithmic Delta power and Slope and seizure length across NC dataset in early post-ictal nights (first two hours). The lines are the fitted coefficients of Linear Mixed Effect Model (LMM) with shaded area representing 95% confidence intervals. The data points are corrected by removing the patient/channel-specific baseline variability (LMM random effect). Seizure length has similar but very minimal significant effect on Delta power (A) and Delta slope (B) in both SOZ an NSOZ channels ($p<0.01$, LMM).

Figure 6. Correlation of Postictal Power with SWA Power and SWA Slope. The top panel shows the distribution of Pearson's r-values from linear fits between postictal power and SWA Power. The bottom panel shows the same for fits between postictal power and SWA Slope. Each data point represents a unique correlation from an individual patient-channel combination; different symbols mark patient identity. In SOZ electrodes, the correlation during postictal nights is significantly weaker and more variable compared to interictal nights (SWA Power: $p < 0.01$; SWA Slope: $p < 0.001$; Wilcoxon rank-sum test).

Tables

Subject	Age (yrs)	Sex	Onset (yrs)	ASM	SOZ	#Days/#Seizures
Seizure Advisory System (NeuroVista Inc.)						
NC-1	35-40	M	5-10	CBZ, LCM, PRP, TPM	nTL; prior ATLE	465/101
NC-2	45-55	M	15-20	CBZ, CLZ, LEV, LCM	nTL, prior ATLE	534/769
NC-3	40-45	M	20-25	LTG, LCM, PHT, RTG	nTL	709/40
NC-4	50-55	F	15-20	LEV, OXC, ZNS	FT	318/897
NC-5	45-50	M	20-25	CBZ, LEV	FT	355/732
NC-6	40-45	M	10-15	LCM, LTG, OXC, VPA	OP	607/45
RC+S^{TM} (Medtronic Plc.)						
mT-1	55-60	F	5-10	GBP, TZP, LGT	mTL	831/542
mT-2	20-25	F	5-10	LCM, CZP,	mTL; prior ATLE	392/15
mT-3	35-40	F	0-5	OXC, LEV	mTL	300/250
mT-4	40-45	F	30-35	CZP, LEV, CNB	mTL	401/59
mT-5	30-35	M	20-25	VPA, LCM	mTL	325/219

Table 1. Subject Demographics. Abbreviations: ASM = Anti-seizure medications, CBZ=carbamazepine, CLZ=clobazam, CZP=clonazepam, LCM = lacosamide, LEV=levetiracetam, LTG=lamotrigine, OXC=oxcarbazepine, PHT = phenytoin, RTG=retigabine, ZNS=zonisamide, SOZ = Seizure onset zone Seizure onset zones: mTL – mesial temporal lobe, nFT – neocortical frontotemporal, nOP – neocortical occipitoparietal, nPT – neocortical parietal-temporal, nTL – neocortical temporal lobe.

Participant	Category	Number of days	Average dropout rate during sleep [%]	Average sleep duration [H]	Mean seizure hour during 24-hour day cycle	Circular variance
NC-1	interictal	267	0.03 ± 0.05	8.29 ± 0.98	16.0	0.61
	postictal	51	0.04 ± 0.05	8.61 ± 1.34		
NC-2	interictal	46	0.11 ± 0.06	8.52 ± 2.04	10.9	0.69

	postictal	26	0.12 ± 0.05	8.87 ± 1.59		
NC-3	interictal	549	0.02 ± 0.03	8.51 ± 2.06	12.7	0.6
	postictal	14	0.01 ± 0.02	8.57 ± 2.65		
NC-4	interictal	43	0.01 ± 0.02	8.43 ± 1.77	2.0	0.72
	postictal	42	0.02 ± 0.03	9.54 ± 1.55		
NC-5	interictal	17	0.00 ± 0.01	9.69 ± 1.31	11.5	0.74
	postictal	118	0.01 ± 0.02	9.53 ± 0.83		
NC-6	interictal	260	0.10 ± 0.06	6.43 ± 1.36	15.1	0.59
	postictal	11	0.09 ± 0.08	6.92 ± 2.08		
mT-1	interictal	7	0.07 ± 0.04	8.37 ± 1.47	17.9	0.62
	postictal	8	0.06 ± 0.05	9.09 ± 1.10		
mT-2	interictal	9	0.13 ± 0.04	8.25 ± 3.92	19.2	0.28
mT-3	interictal	8	0.07 ± 0.03	9.07 ± 0.63	15.6	0.7
	postictal	6	0.07 ± 0.03	9.51 ± 0.48		
mT-4	interictal	13	0.07 ± 0.02	9.81 ± 0.83	14.4	0.43
	postictal	1	0.07	9.70		
mT-5	interictal	4	0.12 ± 0.02	7.28 ± 1.62	12.0	0.64
	postictal	1	-	-		
Total	**interictal**	**1223**				
Total	**postictal**	**278**				

Table 2. Nights included in analysis. Total number of analyzed nights in both categories (interictal and postictal) included in analysis for each participant. This includes number of nights taken into the analysis as well as average drop-out of the data, sleep duration, and average seizure hour of the day with its circular variance for each patient and the category.

	mT + NC			
	Interictal	Post-Ictal	p-value	Cohen's d
Total Sleep	8.43 ± 0.29	8.83 ± 0.30	0.007	-0.24
NREM	5.69 ± 0.29	6.03 ± 0.29	0.000	-0.34
REM	1.67 ± 0.20	1.47 ± 0.21	0.020	0.20

715

716 **Table 3. Changes in postictal sleep length.** Using combined data from both cohorts, a
717 postictal sleep is longer for about ~24 minutes than interictal sleep ($p<0.01$). The NREM
718 sleep is longer for about ~21 minutes on average in nights after seizures compare to
719 interictal nights ($p<0.001$), while the REM sleep is about ~12 minutes on average shorter
720 ($p<0.05$). P-values and Cohen's d were calculated using a Linear Mixed Model (LMM).

721

722

723

			Early Night				Late Night			
		Delta	Interictal	Post-Ictal	ratio	p	Interictal	Post-Ictal	ratio	p
NC	NSOZ	Power μV²/Hz	184 ± 23	219 ± 28	0.84	0.000	160 ± 20	174 ± 22	0.92	0.000
	SOZ		346 ± 40	427 ± 50	0.81	0.000	301 ± 35	339 ± 39	0.89	0.000
	NSOZ	Slope μV/sec	272 ± 15	299 ± 16	0.91	0.000	261 ± 14	271 ± 15	0.96	0.000
	SOZ		366 ± 18	412 ± 20	0.89	0.000	352 ± 17	374 ± 19	0.94	0.000
mT	SOZ	Power μV²/Hz	1461 ± 437	1528 ± 458	0.96	0.028	1113 ± 333	1137 ± 340	0.98	0.161
	SOZ	Slope μV/sec	850 ± 160	911 ± 171	0.93	0.000	727 ± 137	741 ± 139	0.98	0.037

Table 4. Changes in Delta band activity during interictal vs postictal nights.

The values are Estimated Marginal Means (EMM) ± standard error for Delta power (μV²/Hz) and Delta slope (μV/s) within the Seizure Onset Zone (SOZ) and Non-Seizure Onset Zone (NSOZ) electrodes, stratified by night period (Early vs. Late). Comparisons are made between interictal nights (without any seizure the same day) and postictal nights (nights after a seizure). The 'ratio' columns represent the interictal EMM divided by the postictal EMM. P-values were calculated from a General Linear Mixed Model (GLMM) using a Gamma distribution with a log-link function. In the NC cohort, this model also revealed a positive significant interaction for SOZ electrodes in postictal nights for Delta power ($p<0.05$) and Delta slope ($p<0.01$). Reported p-values reflect post-hoc pairwise comparisons between the interictal and postictal states, adjusted using the Tukey method.

	Delta power	Delta slope	Sleep duration	NREM duration	REM duration
Estimated Coefficient Seizure Length	0.00034	0.07019	0.00125	0.00057	0.00026
Standardized Coefficient **(β)** [95% CI]	0.04 [0.01-0.06]	0.05 [0.02-0.08]	-	-	-
p-value	<0.01	<0.001	n.s.	n.s.	n.s.

Table 5. Effect of seizure length on sleep duration and slow-wave dynamics in NC cohort. Results from a Linear Mixed Model (LMM) assessing the effect of seizure length on postictal Delta power, Delta slope, and sleep stage durations. The LMM shows a minimal effect size for seizure length on electrophysiological markers (Delta power and slope) and a non-significant effect on total sleep, NREM, and REM sleep durations.