Seizure: European Journal of Epilepsy 85 (2021) 145–150

Contents lists available at ScienceDirect

Seizure: European Journal of Epilepsy

journal homepage: www.elsevier.com/locate/seizure

Does glucose influence multidien cycles of interictal and/or ictal activities?

Alexa Pappas [a], Sanjay Kubsad [b], Maxime O. Baud [c,d], Kyla E. Wright [e], Devon M. Kollmyer [f], Nicole M. Warner [b], Alan M. Haltiner [b], Ryder P. Gwinn [b], Michael J. Doherty [b,*]

[a] University of Southern California, Dornsife College of Letters, Arts, and Sciences, Los Angeles, CA, USA
[b] Swedish Epilepsy Center, 550 17th Ave suite 540, Seattle, WA, 98122, USA
[c] Wyss Center for Bio and Neuroengineering, Geneva, 1202, Switzerland
[d] Sleep-Wake-Epilepsy-Center, Department of Neurology, Inselspital, University Hospital, University of Bern, Bern, 3010, Switzerland
[e] NYU School of Medicine, New York, NY, USA
[f] Western University of Health Sciences, Lebanon, OR, USA

ARTICLE INFO

Keywords:
Biomarker
Interictal
Prediction
Stimulation
Multidien, circadian

ABSTRACT

Purpose: There are multidien patterns of seizure occurrence. Predicting seizure risk may be easier with biomarker correlates to multidien patterns. We hypothesize multiday hyper or hypoglycemia contributes to seizure risk.
Methods: In a type I diabetic (T1D) with focal onset epilepsy with continuous glucose monitoring (CGM) and responsive neurostimulation (RNS) devices, we studied multiday interictal activities (IEA), seizures, and glucose. Hourly CGM data was matched to hourly RNS captures of interictal and ictal activities over 33 months. RNS detection settings were unchanged. Multidien cycles were analyzed, active blocks of IEA and ictal episodes defined, and tissue glucose averages studied.
Results: Average glucose was 161 mg/dl. A 40-day cycle of interictal and ictal activities occurred, though no similar glucose cycle was evident. Glucose elevations relative to patient average were associated with increases in IEA but not seizure. Frequent seizures were not associated with obvious elevations or decreases of glucose from baseline, most seizures occurred at +/- 10 mg/dl of average daily glucose (i.e. 150−170 mg/dl).
Conclusion: Tissue glucose may influence IEA but may not influence multiday seizure activity or very frequent seizures. In an ambulatory T1D patient multiday hypo or hyperglycemic extremes do not appear to provoke seizure activities.

1. Introduction

Studies of epilepsy surveillance systems, ictal and interictal epileptiform activities (IEA) show circadian and multidien patterns, with multiday patterns of rising phase IEA suggesting seizures are more likely [1–4]. IEA are non-ictal patterns that Responsive Neurostimulation Systems (RNS) may detect via surveillance EEG, patterns could include spikes, repeated sharp waves, polyspikes and fast oscillations [3,5]. Biomarker studies might clarify how RNS evident mulitidien IEA and ictal risk are related [4,6,7].

Epilepsy biomarker studies include reactive oxygen species (e.g. cyclooxengenases), hypoxia markers (e.g. glutamate or hypoxia inducible factor 1), immune and inflammation related micro RNA expression, or both cytokine and complement systems [6,7]. These studies focus on epileptogenesis. Different biomarker studies focus on *ictogenesis*, or how might seizures be triggered? Human biomarker studies of ictogenesis need to be practical with surveillance technologies available, safe and reliable, and most importantly, somehow *time linked to both long and short durations of reliable seizure documentation* [4,5,8].

Continuous glucose monitoring (CGM) records 5-minute tissue glucoses, that data helps manage type 1 diabetes (T1D). We studied a T1D patient with focal-onset epilepsy with CGM *and* RNS to identify relationships between glucose and seizure, initially by time and location of seizure, and later how IEA and seizures map over an average 24 -hs [5,8]. We found tissue glucose showed inverse relationships to IEA, with a predilection for seizure to occur when IEA were increasing. In addition, left vs right-onset seizures occurred at different times and tissue glucoses, suggesting possible anatomically localized circadian variance in glucose pathophysiologies. We concluded tissue glucose might influence ictal and/or IEA risk in a time-dependent manner. A follow up hypothesis, in light of RNS evident multidien patterns of seizure, would be if glucose effects on IEA or ictal activity were apparent over long multidien

* Corresponding author.
E-mail address: Michael.doherty@swedish.org (M.J. Doherty).

https://doi.org/10.1016/j.seizure.2020.12.002
Received 8 September 2020; Received in revised form 4 December 2020; Accepted 6 December 2020
Available online 13 January 2021
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cycles [4].

In a series of CGM- monitored T1D patients *without* epilepsy, mulitdien glucose variabilities were seen over 3 menstrual cycles. [9] We don't know what multidien cycles of glucose are in patients without diabetes let alone with epilepsy. Pre-CGM-era literature suggests seizures are likely in acutely ill patients with hyper or hypoglycemia. This literature is based around glucose checks performed largely after seizure occurrence. We hypothesize that multidien durations of hyper or hypoglycemia might promote ictal activities [10–15]. Here we study 33 months of CGM and RNS data from the same T1D patient to determine if multiday cycles of ictal, IEA, or glucose activity occur.

2. Methods

With informed consent, continuous RNS and CGM (Dexcom) data spanning October 2016-July 2019 were studied from a single patient with T1D and focal onset epilepsy. RNS detection settings were unchanged, and her CGM calibrated for accuracy multiple times a day. IEA detections and seizure onsets were recorded from hippocampi (Supplemental Fig. S1). RNS and CGM data were matched by day, month, year and hour. Seizure diaries along with epilepsy board-certified assessment of available electrocorticography (EEG) of RNS-defined *long episodes* (events that provoked at least 5 stimulations to stop ongoing abnormal activity within 90 s) were classified as left or right origin ictal (seizure), or uncertain episodes according to examples in Supplemental Fig. S1. Uncertain episodes were extremely frequent or sustained runs of *non-evolving* IEA. A seizure was classified as unilateral or bilateral dependent on corticography evident spread patterns. As diary entries were dated, but not necessarily by hour, they were matched to time of most likely recent long episode. Menstrual variability was not studied due to insufficient diary.

2.1. Multidien analysis combining ictal and IEA and Multidien glucose cycle verification

Multidien cycles of glucose, IEA and seizure were assessed using time-frequency analysis, decomposing hourly IEA and glucose time-series into different rhythms and extracting the power and phase of possible multidien rhythms between 7 and 50 days using Matlab's wavelet toolbox [1]. Ictal events were related to IEA (continuous variable) via phase analysis and plotted both by left or right onset as well as by diary classifications of loss of awareness or not.

2.2. Multidien Ictal- active vs quiet comparisons

Independent of wavelet analysis, seizures were noted to sometimes occur frequently over short multi-day durations (i.e. an active cycle) or occur isolated from other events (i.e. a quiet cycle). Duration between episodes allowed a dichotomization into *active* or *quiet* cycles. The most frequent interval between long episodes was 3.8 days. If a maximum of 4 consecutive days passed between episodes, both would be classified *active*. Multiple episodes within 24 h were counted in active cycle. If episodes occurred in intervals longer than 4 days from the last (or next) episode, they were designated *quiet*. Average hourly glucose for active vs. quiet comparisons were T-tested, some events did not have corresponding hourly glucose. Regardless of glucose levels, lateralized ictal onsets were also tested for active vs. quiet tendencies (Chi-square)

2.3. Multidien IEA- active vs quiet comparisons

IEA analysis shows consecutive days where detections were significantly higher (or lower) than average. Detections occur hundreds to thousands of times a day, dichotomizing active vs quiet epochs of IEA was via Z-scoring detection number variance. IEA epochs were deemed *active* if Z scoring was $\geq$1 for four-subsequent days, if Z scores were $\leq$-1 for four consecutive days the epoch was *quiet*. Remaining Z scores were *neutral*. Daily average glucose comparisons between active, quiet and neutral IEA were T-tested.

2.4. Long episode mismatches

The RNS records long episodes in two ways, counting occurrence, and saving EEG. Four long episode EEG per upload are stored before episode data is overwritten. If six long episodes occurred between RNS uploads, only the last four would be available to review. All six would be recorded as "long episodes" but only four would have EEG. If mismatches between long episode number and available EEG are apparent, we would undercount episodes, particularly if episodes are frequent and RNS uploads are not. Without accounting for missing long episode EEG, undue emphasis on findings might occur. Descriptive statistics were used to acknowledge these mismatches.

3. Results

3.1. Epilepsy and type I diabetes history

At study onset, the patient was 45 years old. Her focal epilepsy manifested with impaired awareness events that could progress to bilateral tonic-clonic seizures. Seizures began at age 19. Seizure triggers include fatigue, stress and menses, though a menstrual pattern was not appreciated in prior RNS-to-diary correlations. Audiogenic triggers could occur, Johnny Cash's *Ring of Fire* reliably provokes a seizure. A brother and paternal second cousin have epilepsy, an epilepsy panel through Ambry genetics, 2018, showed normal LG1 (this gene is associated with audiogenic seizure) and a DYRK1A gene variant of unknown significance at p.H106R.

During one week of the study period, an elevated anti GAD antibody titer unassociated with clinical stiff-person syndrome was treated with intravenous immunoglobulin (IVIG) therapies without clinical betterment in epilepsy or other medical complaints in the ensuing month(s), RNS measures during IVIG course were similar to baseline. Failed antiseizure therapies include levetiracetam, topiramate, clobazam, clonazepam, lamotrigine, phenytoin, phenobarbital, pregabalin, carbamazepine, felbamate, brivaracetam. A vagus nerve stimulator trial failed, the device was programmed off a decade prior. She remained on levetiracetam, topiramate and clobazam, those medications were used in the study period with minimal dose adjustments. Intracranial monitoring showed hippocampal depth onset for left seizure and an independent right temporal seizure though not more discretely localizable. RNS detection and stimulation electrode placements were thought to be most useful from bilateral hippocampi. After RNS placement, her device was optimized for detection and stimulation settings and these were unchanged during the study period.

T1D was diagnosed at age 31, well after her epilepsy began. Complications include gastroparesis and hypoglycemia unawareness. A continuous insulin pump was used during the study period, her pump required manual inputs to respond to glucose variance, insulin changes and dosing data was not available.

3.2. General findings

Fig. 1 shows IEA, ictal activities and long episodes represented on a timeline that includes the study period. Table 1 shows findings of the varied glucose levels based on event and active vs quiet classifications along with statistical testing. Average mean glucose was 161 mg/dl, median was 157 mg/dl. Hemoglobin A1C ranged from 6.4 to 7.1% with an average of 6.8 % (reference range 4–6 %).

3.3. Multidien rhythm analysis: combining Ictal and IEA

Wavelet analysis showed periodicity best at approximately 40 days, with left and right sided hippocampal IEA peaking in-phase (Fig. 2). Left

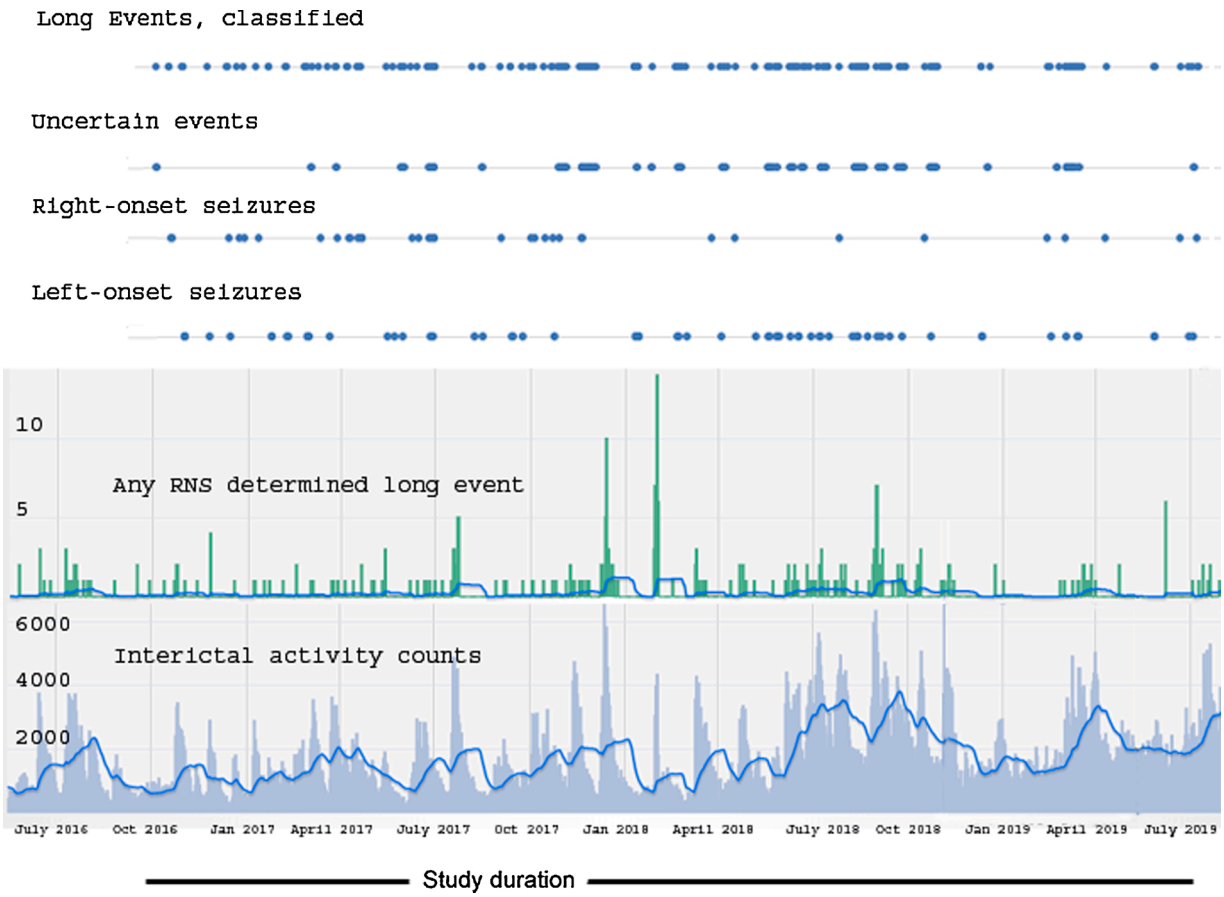

Fig. 1. Plots over entire study period of various Responsive Neurostimulation defined long episodes, and interictal activities, IEA. Active epochs of IEA are perhaps easiest to see as peaks on the histogram in light blue (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

onset seizures strongly correlated to the rising phase of IEA (phase locked variable, PLV = 0.54, p <0.01) (Fig. 2) whereas right onset seizures did not (PLV = 0.13, p = 0.57). 40-day (or other duration) multidien glucose cycles *were not* seen and no glucose influence on long-duration IEA or ictal cycles noted.

3.4. Multidien Ictal- active vs quiet comparisons

Ictal activity classified as *active* had higher (159 mg/dl) glucose than *quiet* (150 mg/dl) though the differences were insignificant (Table 1). Left seizure onsets had higher glucose than right, these differences were insignificant. However if classified by side of onset and quiet vs active alone (i.e. independent of glucose), lateralized differences were significant (X^2, p < 0.01).

3.5. Multidien IEA active vs quiet analysis

Days when IEAs were active (Z–score ≥ 1, n = 155 days) had an average glucose of 167 mg/dl compared to when quiet, (Z-score ≤-1, n = 129 days), glucose was 152 mg/dl (p < 0.001). Active IEA epochs were incidentally noted to also include 18 of 99 ictal events (19 % of total events: 14 left, 4 right) and 50 of 70 (71 %) of unclear episodes. Quiet IEA epochs showed 5 of 96 (5%, 3 left and 2 right) ictal events and 0 of 70 (0%) of unclear events. The remaining ictal events (n = 76) and unclear episodes (n = 20) occurred when -1> Z-score < 1 at an average glucose of 161 mg/dl.

3.6. Long episode mismatches

The RNS recorded 279 long episodes, though only 182 had EEG present (65.6 %), 178 of which were classified (four back-to-back "long episodes" were continued observances of an invariant non evolving IEA). Mismatches were seen on 40 days, 130 long episodes occurred, 33 had EEG. The 97 remaining long episodes *without* EEG showed average hourly glucose of 171 mg/dl.

3.7. Patient diaries

Of RNS evident seizures, 26 % were patient-identified as seizures, 16 of 66 left,10 of 38 right origin. Of patient identified seizures, regardless of EEG capture or not (n = 74), glucose averaged 161 mg/dl. Of 74 RNS-evident uncertain episodes, only one was possibly identified as seizure in her diary. The majority of remaining diary entries were unassociated with *any* episode e.g. "feel like having a seizure" or "slight seizure temptations" or "I feel close to seizures" and may have represented auras, overwritten event data from RNS, or symptomatic hyper or hypoglycemia, though no consistent glucose elevation or diminishment was seen.

4. Discussion

In this patient with T1D, glucose average was elevated at 161 mg/dl. We were *unable* to show that seizures are more likely when at the extremes of her glucose range. Most seizures occurred in a state of mild hyperglycemia i.e. in a 150−161 mg/dl range, though for her, a range which might be considered her homeostatic norm. Very frequent runs of

Table 1
Glucose relationships to ictal, interictal activity (IEA) and glucose.

	Average glucose,mg/dl	SD	*t* -test comparison, result
Basic findings			
Mean daily glucose (n = 977 days)	161 (range 66–343.2)	35.0	
Median daily glucose (n = 977 days)	157 (range 50–340)	40.4	
Average hourly glucose (21,805 available)	161 (range 40–419)	64.6	
All long episode with glucose, n=163	162 (range 55–341)	62.2	
All ictal with glucose, n=94	157 (range 62–310)	56.12	
Uncertain episodes with glucose n=69	170 (range 65–341)	70.0	Uncertain episodes vs. all ictal, t = 1.24, $p = 0.21$
Left ictal n=63	161 (range 62–310)	56.7	
Right ictal n=31	150 (range 55–243)	57.3	Left vs. right ictal, t = 0.79, $p = 0.48$
Unilateral ictal, n=56	154 (range 55–264)	58.8	
Ictal spread bilaterally n=38	162 (range 62–310)	52.1	Unilateral vs. bilateral ictal, t = 0.70, $p = 0.43$
Active vs. Quiet Epochs			
Active Ictal, n = 75 (56 left, 19 right)	159 (162 left, 153 right)	56.0	
Quiet ictal, n = 19 (7 left, 12 right)	150 (152 left, 148 right)	57.4	Active vs. quiet ictal, t = 0.67, $p = 0.50$
Active uncertain episode, n=64	174 (range 66–341)	69.9	Active uncertain vs. all ictal: t = 1.35,$p = 0.18$
Quiet uncertain episode, n=5	117 (range 65–184)	48.4	
Active IEA, Z > 1 (n = 155 days)	167 (range 93–293)	39	Active vs. quiet IEA: t = 3.43, $p = <0.01$
Quiet IEA, Z <-1 (n = 129 days)	152 (range 93–264.5)	33	Neutral vs. active IEA: t = 1.72, $p = <0.09$
Neutral IEA -1 ≤ Z ≤ 1 (n = 693 days)	161 (range 66–343)	35	Neutral vs. quiet IEA: t=-2.7, $p = <0.01$

IEA (i.e. uncertain episodes) are likely with elevations in glucose. Interestingly, when trying to define cycles of events, both the wavelet and ictal active vs quiet analysis suggest there may be *glucose-independent* lateralized tendencies for cyclic event occurrence, in particular for left temporal seizures.

4.1. Type I diabetes and seizure controls

Hyper or hypoglycemia are listed as a risk for seizure occurrence. [10–15]. In this patient, glucose may yet effect seizure provocation in shorter timeframes, perhaps within hours [5,8]. Alternatively, the average glucose, at 161 mg/dl, remains too high to study if hyperglycemia triggers seizures or not, as long-duration states of conventional normoglycmia (e.g. 95−105 mg/dl) were not seen. In this patient, future CGM to insulin pump technologies (i.e. closed loop "artificial pancreas" systems that auto-adjust insulin to effectively diminish glucose means and variability) might permit normoglycemia and clarification if that true hypoglycemic or hyperglycemic states change ictal risk [16].

Whether RNS could also provide input to glucose control systems remains to be seen. In this patient, when her RNS documents active IEA, that data could be seen as clinically relevant, not for seizure provocation, but perhaps more for hyperglycemia variance management.

A different way to study IEA or ictal changes relative to glucose over multidien periods could occur independent of CGM. The glycation of hemoglobin (HgbA1C) reflects 2–3 months of glucose levels [15]. For many diabetics the HGBA1C represents a risk assessment, the higher it is, the more likely microvascular, retinal, cardiac and other compromises are to occur. Lowering to 6.5 % (48 mmol/mol) or less remains a consistent therapy goal. Looking at this patient's various HgbA1c (range 6.4–7.1 in this study period) epochs might permit a different look at multidien variance based on changes in mean glucose level over months.

4.2. Pathophysiologic speculations and future clinical directions

With a limited N-of-1 study and no obvious multidien influence on seizure provocation, glucose is probably not a leading candidate for understanding ictal triggers over long time periods. Further study should address whether hyper and hypoglycemia truly are provocative of seizure in broader populations. Perhaps the best way to study this in non-diabetic patients where CGM and RNS use could eliminate issues similar to this patient's confounding hyperglycemic homeostasis. Another population to study could be people with epilepsy treated with ketogenic diet (KD). Specifically, could CGM along with biomarkers assessing ketotic states (e.g. urine strip tests for ketosis which many KD patients already use) and continuous RNS data better define ictal risk and IEA patterns? This particular study could help map if altering glucose variance in KD patients lowers seizure burdens.

Spencer et al. showed circadian *and* location IEA variance without necessarily provoking seizure, they noted IEA were more prevalent at night and/or sleep [3]. The finding that IEA vary markedly with glucose, location and circadian cycles remains fascinating. An analogy for IEA might be sparks in an electrical circuit. We are used to the idea that sparks trigger fire, and yet, abundant sparks, or in this case very frequent IEA, do not trigger seizure in our patient. If IEA are *not* epileptic phenomena, are they instead some attempt at signaling or switching localized network pathways or anatomies on or off in a glucose dependent manner? Are increased IEA a biomarker of physiology or at what point do they suggest pathophysiology? Might their absence or presence have implications for memory or changes like hypoglycemic unawareness or hyperglycemic associated cognitive declines in diabetics [17]? Might IEA variance, either by circadian timing or with glucose elevations, suggest arousal switch contributions to states like post-prandial fatigue and somnolence? Or broader still, are IEA present and somehow associated with cognitive declines or other pathologies in anyone, let alone diabetics or people with epilepsy?

5. Conclusion

Multidien IEA may increase with glucose elevations, though ictal activities do not. Glucose levels that alter seizure risk may be more important in shorter time cycles, or when a more conventional normoglycemic baseline is betrayed. CGM and RNS devices permit correlative study of tissue glucose with electrophysiologic data over long durations.

Ethical statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

CRediT authorship contribution statement

Alexa Pappas: Conceptualization, Data curation, Formal analysis, Data curation, Investigation, Methodology, Software, Writing - review & editing. **Sanjay Kubsad:** Conceptualization, Data curation, Formal analysis, Data curation, Investigation, Methodology, Software, Writing - review & editing. **Maxime O. Baud:** Formal analysis, Investigation, Methodology, Software, Writing - review & editing. **Kyla E. Wright:** Conceptualization, Data curation, Formal analysis. **Devon M.**

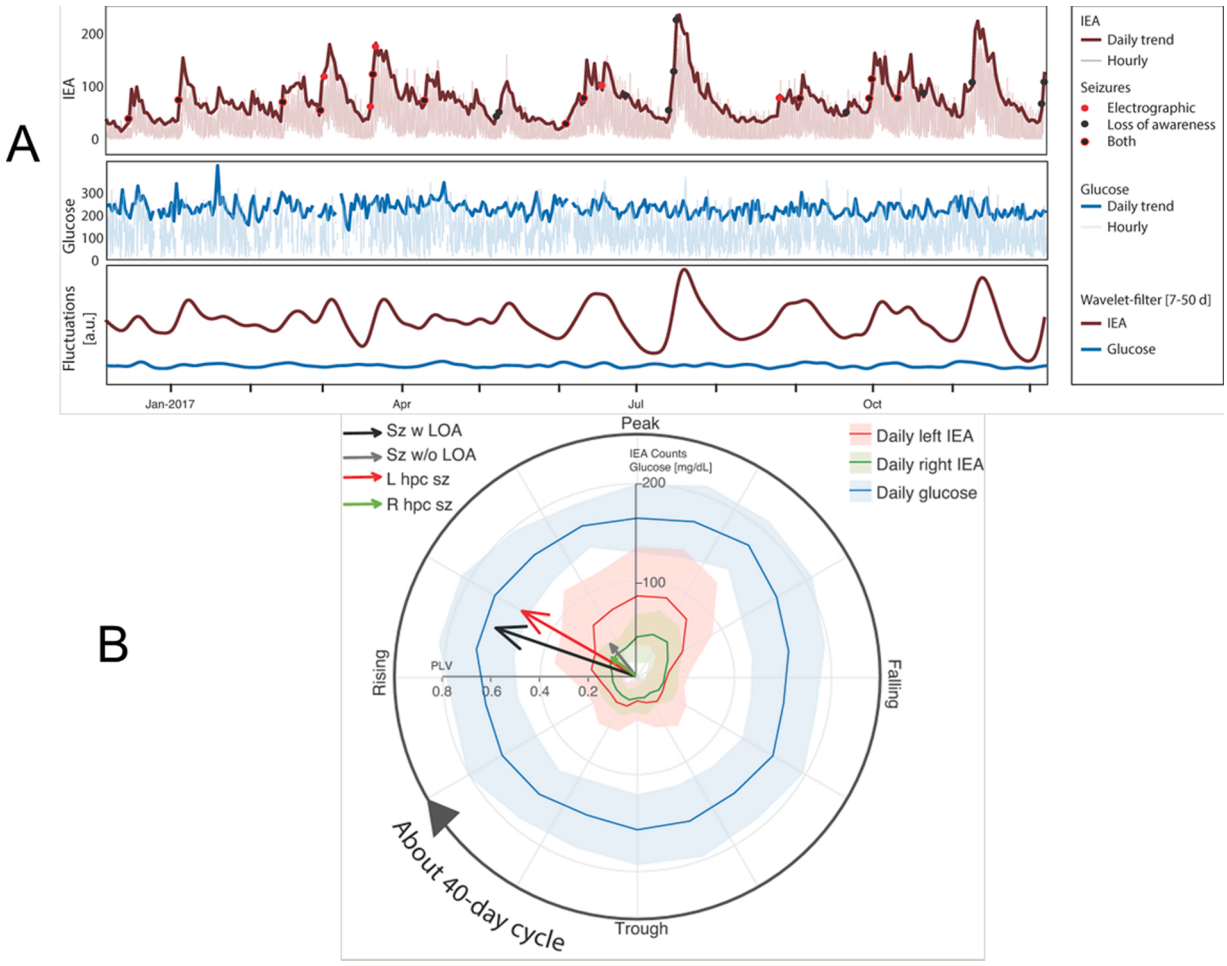

Fig. 2. A. One year of representative cyclic data December 2016-December 2017. Top: Multidien fluctuations of IEA are visible in daily averages (thick line). Seizures, both electrographic and clinical tend to occur in the raising phase of daily IEA fluctuations. Middle: glucose also showed fluctuations over multiple days although with much smaller magnitude. Bottom: multidien rhythm with varying period-length appear in the IEA time-series, but do not correspond to variations in glucose over multiple days. **B**. Multidien rhythms of Interictal activities (IEA) were found with a periodicity dominating at about 40 days. Daily IEA measured in the left and right hippocampus peaked in phase. Seizures recorded electrographically in the left hippocampus occurred preferentially in the raising phase of IEA with a strong clustering (Phase Locking Value ~0.6, $p < 0.01$). Conversely seizures in the right hippocampus did not show a strong preferential phase (Phase Locking Value < 0.2, $p = 0.57$). Daily average blood glucose was uniformly distributed over multidien cycles of epileptic brain activity.

Kollmyer: Conceptualization, Data curation, Formal analysis. **Nicole M. Warner:** Data curation, Investigation, Methodology, Software, Writing - review & editing. **Alan M. Haltiner:** Formal analysis, Methodology, Writing - review & editing. **Ryder P. Gwinn:** Writing - review & editing. **Michael J. Doherty:** Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

Sanjay Kubsad, Alexa Pappas, Kyla Wright, Devon Kollmyer as well as Drs. Michael Doherty and Alan Haltiner have no disclosures. Nicole Fortier, ARNP and Dr. Ryder Gwinn received support from, and/or has served as a paid consultant for NeuroPace. Dr. Maxime Baud is a coinventor on a US Provisional Patent titled “Neural Interface System” filed under ref. no. (62/).

Acknowledgement

Derek Schulte from Neuropace for help with data access.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.seizure.2020.12.002.

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