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Forecasting seizure risk in adults with focal epilepsy: a development and validation study

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1	Forecasting seizure risk in adults with focal epilepsy: a
2	development and validation study
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## 21 Research in context

22

#### 23 Evidence before this study:

24 We searched the literature on seizure prediction in MEDLINE from January 1, 1946, to June 1, 25 2020, in Embase from January 1, 1974, to June 1, 2020, and in Google Scholar (first 200 relevant 26 references) using comprehensive electronic search strategies combining terms "epilepsy", 27 "seizures", "prediction", "forecasting", "cycles", "patterns", "circadian", and "multidien", with no language restrictions. Identified studies used different outcome measures, but most involved 28 29 analyses of electroencephalography (EEG) to predict seizures minutes in advance, with variable 30 success. A single prospective trial of an implanted device for chronic EEG demonstrated above-31 chance accuracy of warnings for imminent seizures in 9 out of 15 enrolled subjects. Two studies 32 in independent cohorts of subjects chronically implanted with intracranial electrodes showed 33 that rates of interictal epileptiform activity oscillate in circadian and multiday (multidien) cycles 34 that help determine seizure likelihood. Circadian cycles and seizure diaries were used in three 35 studies to forecast seizures over short horizons, but we found no results on forecasting seizures

- studies to forecast seizures over short horizons, but we found no results on forecasting seizures
- 36 several days in advance.
- 37

#### 38 Added value of this study:

- 39 In a large cohort of people with drug-resistant focal epilepsy who had chronic EEG recorded by
- 40 an approved clinical device, we demonstrate that circadian and multidien cycles can be
- 41 leveraged to forecast seizures up to three days in advance in some subjects and 24 hours in
- 42 advance in the majority of subjects. These results highlight the feasibility of seizure forecasting
- 43 over horizons longer than previously possible.
- 44

### 45 Implications of all the available evidence:

- 46 Seizures are not entirely random events. Using cyclical patterns of brain activity to forecast
- 47 seizures hours to days in advance may enable novel seizure warning systems and prevention
- 48 strategies. Convergence of findings from multiple independent datasets suggests the
- 49 generalizability of this approach in people with epilepsy, though this will require direct testing in
- 50 prospective clinical trials.

# 51 Abstract

52

## 53 Background

- 54 For people with epilepsy, much suffering stems from the apparent unpredictability of seizures.
- 55 Recently, converging evidence from studies using chronic electroencephalography (cEEG)
- 56 revealed that brain activity in epilepsy demonstrates robust cycles, operating over hours
- 57 (circadian) and days (multidien), which help determine fluctuating seizure risk. We hypothesized
- 58 that cycles of brain activity can be leveraged to estimate future seizure probability, and we
- 59 tested the feasibility of forecasting seizures days in advance.
- 60

# 61 Methods

- 62 This feasibility study involved retrospective analysis of cEEG (≥ 6 months; recorded between
- 63 January 2004 and May 2018) collected with an FDA-approved implanted device in 175 adults
- 64 with drug-resistant focal epilepsy followed at 35 centers across the USA. In distinct
- 65 development and validation cohorts, subjects had  $\geq$  20 electrographic and disabling clinical
- 66 (self-reported) seizures, respectively. In all subjects, the device stored interictal epileptiform
- 67 activity (IEA) that revealed cycles of abnormal brain activity. Point process statistical models
- 68 trained on initial portions of each subject's data generated forecasts of seizure probability that
- 69 were tested on subsequent unseen data and evaluated against surrogate time-series. The
- 70 primary outcome was the percentage of subjects with forecasts showing improvement over
- 71 chance (IoC).
- 72

## 73 Findings

- 74 Models incorporating information about IEA cycles generated daily seizure forecasts with IoC in
- 75 15/18 (83%) subjects and 104/157 (66%) subjects in the development and validation cohorts,
- respectively. In many subjects, the forecasting horizon could be extended up to three days.
- 77 Hourly forecasts, possible only in the development cohort, showed IoC in 18/18 (100%)
- 78 subjects.
- 79

# 80 Interpretation

- 81 Seizure probability can be reliably forecasted days in advance using data from an approved
- 82 device. For adults with focal epilepsy, personalized risk-stratification over days is
- 83 unprecedented and may enable novel seizure prevention strategies. This study paves the way
- 84 for prospective clinical trials that will establish how people with epilepsy may benefit from long-
- 85 horizon seizure forecasting.
- 86
- 87 Funding
- 88 None.

### 89 Introduction

90

Epilepsy is defined by the seemingly random occurrence of spontaneous seizures.
 Although seizures are typically brief events that cumulatively amount to a small fraction of time,
 their unpredictability necessitates standing treatments and causes significant disability.<sup>1</sup> People
 with epilepsy are plagued by constant uncertainty, and the looming threat of seizures has
 implications for personal safety, independence, and psychological well-being. Reliable methods
 to anticipate seizures would mark a paradigm shift in clinical epilepsy, mitigating this
 uncertainty and enabling time-varying, risk-based seizure prevention strategies.

98 Despite decades of progress in the field of seizure prediction, such methods remain 99 elusive.<sup>2</sup> The landmark NeuroVista trial<sup>3</sup> demonstrated feasibility of a cEEG-based advisory 100 system that warned of seizures minutes in advance. Subsequent analyses<sup>4-10</sup> of data from this 101 trial yielded numerous transformative insights that propelled the field for years. However, 102 limitations of these pioneering efforts include the relatively small size of the trial—ten subjects 103 participated in the seizure advisory phase—and the fact that the implanted device used is no 104 longer available.

105 In the decade since the NeuroVista trial, cEEG from another device (RNS® System), one that is FDA-approved and increasingly used in clinical care for epilepsy,<sup>11</sup> revealed pervasive 106 daily (circadian<sup>12,13</sup>) and multi-day (multidien<sup>13</sup>) cycles of interictal epileptiform activity (IEA) 107 that are biomarkers of seizure risk.<sup>13</sup> With these long-timescale biomarkers,<sup>14-16</sup> interest has 108 recently shifted to probabilistic approaches to seizure forecasting,<sup>5,17,18</sup> akin to weather 109 110 forecasting, which leverage prior knowledge about cyclical patterns of seizure risk to estimate 111 seizure probability over future time horizons. Since most prior work in the field has sought to identify seizure precursors in the minutes preceding seizure onset,<sup>2,8</sup> an unresolved question 112 concerns whether periods of heightened seizure risk (pro-ictal states<sup>18</sup>) can be anticipated over 113 114 longer horizons. We hypothesized that seizure probability is determined by alignment of cyclical influences at multiple timescales as well as the temporal distribution of recent seizures.<sup>4,9,10,18</sup> 115 116 Models that incorporate these factors to generate seizure risk forecasts will ultimately require 117 validation in large, prospective clinical trials. Imminent feasibility of such trials hinges on 118 evaluating how generalizable and valuable the approach may be on existing cEEG data, using a 119 probabilistic framework that accounts for the fact that seizures may not occur every time risk is 120 accurately forecasted to be high. 121 Here, we address these questions in a feasibility study aimed at developing and

validating statistical models to forecast the individual risk for electrographic and self-reported
 seizures based on temporal features extracted from up to ten years of cEEG data. The primary
 study outcome was the percentage of subjects for whom forecasting models demonstrated
 Improvement over Chance (IoC) at different forecasting horizons. Secondary outcomes involved
 quantifying model performance using statistical methods suitable for probabilistic forecasts.

## 129 Methods

130

## 131 Study design and participants

This feasibility study involved development of seizure forecasting models in a 'development 132 133 cohort' of 18 subjects who were implanted with the RNS® System (NeuroPace, Inc., Mountain 134 View, CA, USA) for clinical indications and followed at two centers (University of California, San 135 Francisco, and California Pacific Medical Center, USA). Forecasting models were subsequently validated by including cEEG data and self-reported seizures obtained from a 'validation cohort' 136 137 of 157 participants in the nine-year long-term treatment trial (LTT) of the RNS System<sup>11,19</sup> that 138 took place between January 2004 and May 2018 across 34 centers in the USA (appendix, pp 10– 139 11; ClinicalTrials.gov identifiers: NCT00079781, NCT00264810, and NCT00572195). All involved 140 centers obtained authorization from their institutional review board to recruit adults with 141 medically-refractory focal epilepsy in the original trials and for subsequent data analysis. 142 Existing cEEG data and seizure logs were screened for eligibility: > 6 months of continuous 143 hourly IEA count data without large gaps and  $\geq$  20 electrographic or self-reported seizures but < 144 50% days with seizures, as the utility of forecasting in individuals with very frequent seizures is 145 likely low.<sup>3</sup> All 175 included subjects provided written informed consent for analysis of their 146 data. 147

#### 148 Procedure

149 The RNS System utilizes customizable algorithms to detect pathological brain activity, as

150 previously detailed.<sup>13</sup> For each subject, IEA time-series from two RNS System detectors

151 (appendix, pp 10–16) were selected for periods of continuous data with stable detection

settings > 6 months. For all subjects, the first few months of cEEG (median [range] 222 d [28–

153 362 d]) after device implantation were discarded to account for time needed by clinicians to

- 154 optimize detection parameters.
- 155

156 Self-reported seizures are the current gold-standard for clinical trials in epilepsy, but

157 electrographic seizures evident on cEEG are more objective and obviate subjects' reporting

biases.<sup>20</sup> Therefore, we examined two types of seizures drawn from distinct, non-overlapping

- 159 cohorts of subjects: (1) Timestamps of electrographic seizures from cEEG in the development
- 160 cohort (N=18), identified through detections of prolonged epileptiform activity exceeding a

161 clinically pre-specified duration, typically 15–40s. For each subject and each period of stable

- detection settings, a Board-certified epileptologist (V.R.R.) verified visually that ≥90% of these
- detections corresponded to electrographic seizures in stored electrocorticograms, as described
- in detail previously<sup>13</sup>; (2) Diaries of self-reported seizures in the validation cohort (N=157),
   recorded by participants in the LTT as number of seizures ('simple motor', 'simple other',
- 166 'complex partial', and 'generalized tonic-clonic') per calendar day. According to the 2017
- 167 International League Against Epilepsy classification, we considered 'complex partial' and
- 168 'generalized tonic-clonic' as the disabling 'seizures with impaired awareness' studied here and

- 169 excluded subjects without disabling seizures. As subjects did not report the time of day for their
- 170 seizures, these data could only be used for daily and not for hourly forecasts.
- 171

#### 172 Statistical analysis

173 Forecasting models: To forecast seizure probabilities—continuous values between 0 (no risk of 174 seizure occurrence) and 1 (seizure occurrence is certain)—we used past IEA, occurrence times 175 of past seizures, and cyclical variables (hereafter, collectively referred to as 'temporal features') 176 as inputs for point process generalized linear models (PP-GLMs). Models were estimated on 177 training data and evaluated on chronologically subsequent test data. PP-GLMs are established tools in neuroscience research<sup>21,22</sup> that provide a flexible statistical framework to evaluate the 178 179 association between sequences of event (seizure) times represented as binary (or count) time-180 series and temporal features upon which event probability may depend. Hourly IEA time-series 181 were available for electrographic and self-reported seizure cohorts, allowing determination of 182 circadian and multidien cycles of epileptic brain activity in all subjects (N=175).<sup>13</sup> We trained PP-GLMs with a log-link function and a conditionally Poisson distribution<sup>22</sup> to output the probability 183 184 of a seizure as a function of these cycles and other temporal features (appendix, pp 9–10) from 185 subject-specific datasets comprising the shorter of 480 d or 60% of the subject's total data. To 186 prevent inflation of our performance metrics (see below) through the well-known phenomenon 187 of seizure clustering, we defined 'seizure-days' or 'seizure-hours' as binary events regardless of 188 the seizure count and used these as training labels. The large amount of previously unseen 189 testing data (Individually: minimum of 40% of data, >800 d in most subjects and up to 8 y; In 190 total: 73% of data with 211,005 d) ensured that the models were not overfit for a small number 191 of seizures and enabled assessment of forecasting performance in a probabilistic framework. 192

Outcomes: Subject-specific forecast performance was quantified on held-out test datasets (i.e. index test) containing unseen seizures (i.e. reference standard: days or hours with self-reported or electrographic seizures) using two complementary metrics that are fully described in the appendix (pp 1–9): (i) for various seizure warning threshold probabilities, the area under the curve (AUC) of sensitivity (proportion of all seizures captured during warning) vs. corrected proportion of time in warning;<sup>23</sup> (ii) Brier skill score (BSS), adapted from meteorology,<sup>5,17</sup> which

199 200

201 Based on these metrics, the primary outcome was Improvement over Chance (IoC), a binary 202 outcome defined at the individual level through comparison of the original AUC to chance-level 203 AUC, calculated from forecasts issued on surrogate data (see Statistical significance).<sup>2,5,8,23</sup> In 204 addition, secondary outcomes involved quantifying individual forecast performance. We 205 calculated the median AUC across subjects with IoC (and the entire cohort) to evaluate 206 discrimination, the goal of a deterministic forecast (do forecasts differ when their 207 corresponding observations differ? see appendix, pp 1–9). AUC depends heavily on forecast 208 horizon and pro-ictal state duration, and AUC is less than 1 even for a reliable forecast 209 (appendix, p 8). This motivated the additional use of the BSS, which assesses model resolution

evaluates performance in relation to a naïve predictor (here, a randomly shuffled forecast).

210 (are different forecasts associated with different outcomes?) and calibration (how close are

- 211 forecasted probabilities to observed probabilities?), the goals of a probabilistic forecast
- 212 (appendix, pp 1–9). Reliability diagrams<sup>5</sup> were used to compare observed and forecasted
- 213 seizure probabilities.
- 214
- 215 Post-hoc analyses: To characterize individualized forecasts in terms of time-varying risk, we
- 216 defined pro-ictal states as periods of time with forecasted probability above the individual
- expected seizure probability (appendix, pp 1–9). Based on these adjusted values, we report the
- average duration of pro-ictal states and the relative risk for seizures in pro-ictal as compared to
- low-risk states. We evaluated the overlap between forecasted probabilities and observed
   seizures as a function of circadian and multidien cycle phases and AUC as a function of the
- strength of seizure cycles, quantified as the phase-locking value (appendix, p 24).<sup>13</sup>
- 222
- 223 Sensitivity analyses: Robustness of our results was assessed by systematically varying the
- amount of training data and the retraining interval (appendix, pp 21–23).
- 225
- 226 Statistical significance: To determine individual chance-level AUCs, 200 surrogates were
- 227 generated for each temporal feature: (1) for the recent seizure, circadian, and weekly
- distribution models, by randomly shuffling the seizure time-series under the null hypothesis
- that the seizure process is memoryless (i.e. events are independent of one another); (2) for the
- 230 IEA-based features, by randomizing phases of underlying cycles, under the null hypothesis that
- 231 seizure timing does not depend on trends in IEA.<sup>24,25</sup> Significance was assessed with a false
- discovery rate (FDR) at  $\alpha$  = 0.05 across all subjects to correct for multiple testing. As a
- supplementary statistical analysis, significance of AUC was assessed by comparing the number
- of seizures correctly identified by the model and by chance for a given fraction of time under
- warning (appendix, p 28).<sup>23,26</sup> Analyses were performed with MATLAB R2019a, R 3·4·4, and
   Python 3·7·4.
- 237

## 238 Role of funding source

- 239 This study received no targeted funding. All authors had full access to data and had
- 240 responsibility for the decision to submit for publication.
- 241

# 242 Data sharing

- 243 Deidentified individual data in the form of IEA counts and electrographic seizures from the 18 244 subjects in the development cohort, as well as code created and used for this paper, will be 245 freely available at **#DOI will be made available upon acceptance#** as of July 1, 2021 for at least 246 20 years. A short explanation of the data is also provided. Original study protocols, statistical 247 analysis plan, and informed consent forms are not available for this retrospective study. Data 248 for the validation (self-reported seizure) cohort is property of NeuroPace, Inc. and is not 249 available.
- 250

## 252 Results

#### 253

254 We collected retrospective cEEG data from two cohorts of subjects implanted with the RNS

255 System (Fig. 1a, mean duration per subject 1484 d, range 227–3502 d). Between January 1,

256 2018 and October 1, 2019, we screened 72 and 256 subjects, and we included 18 and 157

subjects in distinct cohorts for forecasting model development and validation, respectively

(flow diagram). The development cohort comprised 10 subjects whose cEEG data we previously
 published<sup>13</sup> but here extended to include two years of subsequent recordings, plus 8 new

published<sup>13</sup> but here extended to include two years of subsequent recordings, plus 8 new
 subjects. The validation cohort comprised a subset of participants in the nine-year RNS System

261 Long-term Treatment Trial (LTT)<sup>19</sup>, from which only limited cEEG data has been published<sup>12</sup>.

262 cEEG data (Fig. 1b) from this cohort was used to validate forecasting models, which were then

tested against the published dataset of self-reported seizures from the LTT<sup>19</sup>. Baseline

characteristics for the two cohorts were similar, with median age 38 [IQR 32–51] and 35 [IQR
25–43], and 44% (8/18) and 47% (74/157) females, respectively, with a preponderance of

266 multifocal and mesio-temporal epilepsies (Table 1).

267 In both cohorts, forecasting models were individually estimated on the first portion of 268 each subject's data, the 'training datasets', and tested on non-overlapping individual 'testing 269 datasets' containing a total of 767 electrographic (median 19% [IQR 13–29] days with seizures) 270 and 27,658 self-reported seizures (median 9% [IQR 5–16] days with seizures) that were 271 previously unseen (see Methods). To forecast seizure probability with horizons of hours to days, 272 models incorporated past IEA, occurrence times of past seizures, and cyclical variables as inputs 273 (hereafter, 'temporal features;' Fig. 1c, Table 2). Individual subjects had excellent 274 correspondence between forecasts and seizures (Fig. 1d-h).

As a primary outcome, and for each temporal feature, we determined which subjects 275 276 might benefit from forecasting with our models by calculating improvement over chance (IoC: 277 AUC relative to chance-level, Table 2). Daily forecasts incorporating information only about 278 recent seizures, weekly seizure distribution, or recent IEA produced IoC less often than models 279 using information from multidien IEA cycles, for which IoC was observed in 15/18 (83%) and 280 104/157 (66%) subjects for electrographic and self-reported seizures, respectively (Fig. 2a; Table 281 2). With multidien IEA cycles alone, the forecast horizon could be extended up to three days 282 while maintaining IoC in 2/18 (11%) and 61/157 (39%) subjects for electrographic and self-283 reported seizures, respectively (Fig. 2b).

As secondary outcomes, we quantified forecast performance for subjects with IoC using two complementary metrics, each addressing a distinct question (appendix, pp 1–9): (i) Area under the curve (AUC, sensitivity vs. corrected time in warning)—How valuable is a forecast given the amount of time spent in warning?, and (ii) Brier skill score<sup>5,17</sup>—How well does the forecast perform relative to a reference strategy (BSS = 1 for perfect forecast; BSS = 0 for no

improvement over a random predictor)? Median AUC was 0.74 [IQR 0.70-0.79] and 0.70 [IQR

290 0.65-0.75], and median BSS was 0.23 [IQR 0.18-0.30] and 0.13 [IQR 0.05-0.20] in the

development (electrographic seizures) and validation (self-reported seizures) cohorts,

respectively (Fig. 2a, c; all median values in Table 2; appendix, pp 17–18). A reliability diagram<sup>5</sup>

showed that resolution (Fig. 2d, highest bin average is below 1) and calibration were good, but
not perfect, with forecasted probabilities above 25% being overconfident (i.e. below the
diagonal line of perfect calibration, Fig. 2d).

296 As a post-hoc analysis, we characterized the durations of forecasted pro-ictal states, i.e. 297 the tendency for daily forecasts to remain high over consecutive days (Fig. 1f). To allow for 298 comparison across subjects, we averaged peak-aligned forecasts centered within subjects 299 around expected seizure probability (appendix, pp 1–9). This enabled visualization of pro-ictal 300 states as contiguous periods of heightened seizure probability lasting 3–9 d and aligning well 301 with the distributions of observed electrographic and self-reported seizures (Fig. 3). Average 302 relative risk (RR) for self-reported and electrographic seizures occurring during forecasted pro-303 ictal versus low-risk states was 9.4 [95% CI 4.5–14.9] and 3.7 [95% CI 2.8–4.7]) across subjects 304 with IoC. Model performance also correlated with phase-locking values between seizures and 305 multidien IEA cycles<sup>13</sup> (Pearson r= $0.6547\pm2.7\times10^{-3}$ , Wald test, p<0.0001; appendix, p 24), 306 suggesting that the most forecastable individuals can be identified in advance.

To further characterize performance of daily forecasts, we carried out sensitivity analyses to inclusion criteria (appendix, pp 19–20) and to training conditions. In both cohorts, longer training duration and iterative retraining (appendix, p 23), improved model performance and the calibration of output forecast probability (Fig. 2d; appendix, pp 21–22).

311 Forecasting days-long pro-ictal states over long horizons may not be ideal for all 312 patients,<sup>27,28</sup> so we asked whether our approach allows refinement of forecasts to shorter horizons. Equivalent outcomes were obtained for hourly forecasting, which was only possible 313 314 for electrographic seizures, as subjects in the validation cohort reported seizure days but not 315 hours. Multivariate models incorporating instantaneous phases of circadian and multidien 316 cycles and the recent circadian distribution of seizures<sup>5</sup> yielded the best-performing hourly 317 forecasts of electrographic seizures (Fig. 4a, c; appendix, p 25), and IoC was observed in 18/18 318 subjects (100%; Table 2; appendix, pp 25–26). The forecasting horizon could be extended up to 319 14 h while maintaining IoC in 8/18 subjects (44%; Fig. 4b). Across subjects, highest forecasted 320 seizure probabilities occurred when critical phases of multidien and circadian cycles aligned (Fig. 321 4d).

322

#### 324 Discussion

325

326 Here, we forecasted electrographic seizures and self-reported seizures—a gold standard metric 327 for clinical trials in epilepsy—up to three days in advance. To our knowledge, this represents an 328 unprecedented horizon for personalized seizure risk-stratification. Daily forecasts were above 329 chance in the majority of the 175 adults with focal epilepsy involved in this feasibility study 330 (15/18 and 104/157 in development and validation cohorts, respectively). In all subjects for 331 whom it was possible (18/18), forecasts of electrographic seizures achieved finer temporal 332 resolution on the scale of hours. Included subjects were treated with an implanted 333 neurostimulation device and may not be representative of all people with epilepsy, though 334 diverse focal epilepsies were represented in our cohorts, and seizure cycles are independent of brain stimulation.<sup>13,15</sup> 335

To date, there has been only one prospective trial (NeuroVista<sup>3</sup>) of a seizure advisory 336 337 system, which provided short-term (minutes) warnings of imminent seizures demonstrating 338 above-chance accuracy in 9 out of 15 (60%) enrolled subjects (10 of these subjects completed a 339 4-month testing period). Subsequent analyses on the same dataset showed that even the most 340 difficult cases were predictable to some extent through crowd-sourced computational efforts.<sup>6-8</sup> 341 In comparison, our feasibility study involved ten times more subjects, testing and validating a 342 single computational approach for periods up to 10 years, and forecast horizons several orders 343 of magnitude longer (hours to days).

344 To evaluate forecasting model performance rigorously, we comprehensively report 345 measurements of risk, discrimination, resolution, and calibration (explained in appendix, pp 1– 346 9). During forecasted pro-ictal states, the average RR of occurrence of electrographic and self-347 reported seizures was 9.4 and 3.7, respectively, placing cycles of epileptic brain activity among 348 the strongest predictors of seizures discovered to date. While RR is a well-established metric in 349 medicine, it is limited to the evaluation of probabilistic forecasts at a single threshold value, 350 whereas the BSS circumvents this limitation, offering a refined interpretation of forecast 351 performance as a continuum (appendix, pp 1–9). A recent study in nine subjects employed probabilistic methods similar to ours within a circadian framework and yielded BSS ranging 352 0.02-0.2 at a forecast horizon of one minute.<sup>5</sup> In comparison, our study provided well-353 calibrated forecasts, as illustrated in a reliability diagram (Fig. 2b), and median BSS of 0.23 [IQR 354 355 0.18–0.30] (electrographic seizures) and 0.13 [IQR 0.05–0.20] (self-reported seizures). Another 356 key distinction of our work is that daily forecasts of higher seizure probabilities were aggregated 357 over days-long pro-ictal states (Fig. 3), providing smooth forecasts rather than flickering alerts 358 based on real-time detection of evanescent seizure precursors. This may improve the 359 interpretability of forecasts for people with epilepsy.<sup>3</sup>

This study has limitations. Implanted devices are associated with surgical risks and may
 not be suitable for all people with epilepsy who desire seizure forecasts, motivating
 development of minimally-invasive methods to monitor seizure risk biomarkers.<sup>1,4</sup> Cycles of IEA
 may be more tractable than biomarkers requiring high sampling rate intracranial EEG,<sup>29</sup> opening

the possibility that certain novel methods, like sub-scalp EEG,<sup>30</sup> could be viable for forecasting.

365 Our models did not incorporate common seizure triggers, such as medication non-compliance, 366 which could account for some apparent 'false negatives.' Self-reported seizure data was drawn 367 from a large, prospective, nine-year clinical trial<sup>11,19</sup>—arguably the most well-curated clinical seizure dataset of this chronicity—but inaccuracy of seizure self-reports<sup>3,20</sup> and small gaps in the 368 369 data could have led to under-estimation of model performance. Finally, to dissect the potential 370 contribution of different temporal features, this feasibility study focused on explicit statistical 371 models that are computationally efficient, modest in their training requirements, and 372 incorporated cycles of IEA using an accurate but non-causal estimation of the instantaneous 373 phases. Thus, conclusions should be regarded as hypothesis-generating rather than clinical 374 evidence.<sup>8</sup> 375 In summary, our results corroborate an emerging view that seizures are not entirely

random events.<sup>8</sup> Given the large sample size, these results validate and powerfully extend our 376 previous findings based solely on electrographic seizures,<sup>13</sup> and they suggest the generalizability 377 of using multiscale cyclical biomarkers in epileptic brain activity to forecast clinically-relevant 378 379 seizures over long horizons. Moreover, our study indicates that seizure forecasting is feasible 380 with existing neurotechnology in widespread clinical use (~3,000 patients currently implanted in 381 the U.S.) and need not await novel industrial developments. Future prospective clinical trials 382 should assess directly the ways in which people with epilepsy benefit from replacing constant 383 uncertainty about seizures with "measured uncertainty" (forecasted risk) at different horizons, 384 which has not been established by this or prior studies. To that end, we propose a nested 385 approach to personalized seizure forecasting: (1) patient-specific multidien cycles reveal pro-386 ictal states days in advance; (2) circadian IEA cycles and peak seizure times reveal hours of high 387 risk;<sup>5</sup> and (3) real-time detections of seizure precursors<sup>2</sup> provide imminent seizure warnings 388 conditioned on prior probability from (1) and (2). Future work will also involve miniaturization of devices, integration of cEEG with multimodal physiological data,<sup>1</sup> optimization of forecasting 389 390 models, and elucidation of mechanisms underlying cycles in epilepsy. 391

# Legends 394

	Development cohort	Validation cohort
N	18	157
Age in years (median [IQR])	38 [32-51]	35 [25-43]
Percent females	44% (8/18)	47% (74/157)
Percent males	56% (10/18)	53% (83/157)
Seizure studied	Electrographic seizures	Self-reported disabling seizures
Bilateral focus	50% (9/18)	46% (73/157)
Left-sided focus	33% (6/18)	39% (62/157)
Right-sided focus	17% (3/18)	14% (22/157)
Mesiotemporal lobe epilepsy	83% (15/18)	64% (101/157)
Frontal lobe epilepsy	0% (0/18)	9% (14/157)
Multilobar epilepsy	6% (1/18)	12% (19/157)
Other neocortical epilepsy	11% (2/18)	15% (23/157)
Percentage of days with seizures	25% [17-29]	15% [10-25]
in training datasets (median		
[IQR])		
Percentage of days with seizures	19% [13-29]	9% [5-16]
in testing datasets (median [IQR])		

**Table 1.** Demographics and seizure characteristics of all subjects in the development and
 

validation cohorts.

		Forecasts								
Horizon		Daily					Hourly			
Cohort		Development (N=18)		Validation (N=157)			Development (N=18)			
Reference		Electrographic			Self-reported			Electrographic		
standard		seizures			disabling seizures			Seizures		
Study outcome		1°	2	•	1° 2°		1°	2°		
	Metric	loC	AUC	BSS	loC	AUC	BSS	loC	AUC	BSS
	Recent	2/18	0.62	0.06	43/157	0.58	0.012	6/18	0.57	0.002
	seizures	(11%)	(0.60)	(0.03)	(27%)	(0.57)	(0.009)	(33%)	(0.52)	(0.00)
	Recent IEA	0/18	NA	NA	51/157	0.62	0.04	5/18	0.64	0.008
		(0%)	(0.61)	(0.02)	(32%)	(0.58)	(0.01)	(28%)	(0.60)	(0.006)
ures	Circadian IEA	NA	NA	NA	NA	NA	NA	8/18	0.65	0.01
	phases							(44%)	(0.62)	(0.01)
eat	Circadian	NA	NA	NA	NA	NA	NA	11/18	0.62	0.008
al f	seizure							(61%)	(0.59)	(0.002)
ors	distribution									
du	Weekly	0/18	NA	NA	0/157	NA	NA	NA	NA	NA
Tei	seizure	(0%)	(0.54)	(0.00)	(0%)	(0.56)	(0.004)			
-	distribution									
	Multidien	15/18	0.74	0.23	103/157	0.70	0.13	15/18	0.70	0.024
	phases	(83%)	(0.73)	(0.17)	(66%)	(0.66)	(0.07)	(83%)	(0.70)	(0.018)
	Multivariate	NA	NA	NA	NA	NA	NA	18/18	0.75	0.036
								(100%)	(0.75)	(0.035)

Table 2. Primary and secondary study outcomes. Percentage of subjects with Improvement
over Chance (IoC) for different temporal features, where IoC was obtained by comparing the
area under the curve (AUC) of the original data with the AUC of 200 surrogate time-series with
alpha < 0.05 adjusted for false-discovery rate correction. Data are median AUC and median</li>
Brier skill score (BSS) among subjects with IoC (entire cohort). 1°: primary, 2°: secondary.





408 Figure 1. Individual seizure risk forecasting in one subject. (a) Responsive Neurostimulation 409 (RNS<sup>®</sup>) System, comprising a cranially-implanted neurostimulator connected to two four-410 contact intracranial depth leads (shown, for example, in hippocampus, red) and/or cortical strip 411 leads (shown unconnected) that provide chronic electroencephalography (cEEG). (b) From these 412 recordings, the RNS System provides hourly counts of detections of interictal epileptiform 413 activity (IEA) and electrographic seizures (not shown). (c-e) Entire test dataset from one subject 414 (S7) showing input temporal features, output daily forecasts, and observed seizures. (c) Time-415 series of IEA averaged over one calendar day ('daily IEA'), underlying multidien cycle, and 416 electrographic seizures that serve as some of the input temporal features for the forecasting 417 model. (d) Daily forecast of seizure probability (gradient-colored lines) at 24-hour horizon (D<sub>+1</sub>) 418 generated by a model (grey arrow) trained on ten months of data (not shown) and run on seven 419 months of held-out test data (shown here) using input variables from c. Higher forecasted 420 probabilities (red) form days-long pro-ictal states (red shadow) during which daily probability of 421 seizures is continuously above the expected probability, defined as the long-term average daily 422 seizure frequency calculated over months of training data ('E', here 0.19 seizures per day). (e) 423 Seizures observed during and outside of pro-ictal states over these seven months. (f) Average 424 pro-ictal state illustrated by peak-aligned average probability forecasts (top) and corresponding 425 temporal distribution of seizures (bottom, shown as stacked individual events and percentage 426 of total count on y-axis). (g) Hourly forecasts of seizure probability based on hourly IEA and its 427 circadian cycle (not shown) refining pro-ictal states into hours of relatively higher and lower seizure risk. BSS: Brier skill score. (h) Seizures observed over this period of nine days. 428





seizure probability vs. binned forecasted probabilities of electrographic seizures (green, N=18

subjects) and self-reported seizures (orange, N=157 subjects). Empirical curves for a set of

447 forecasts generated by models before (empty dots) and after (filled dots) re-training after every

seizure are compared to the dashed diagonal line of perfect calibration (shading indicates 95%

449 confidence intervals (CI)).

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452

453 Figure 3. Pro-ictal states. (a) Peak-aligned normalized average forecast probabilities for all 454 subjects in the electrographic seizures (development) cohort (N=18, rows, ranked by width of 455 pro-ictal state) reveal days-long periods of seizure probability higher than the expected seizure 456 probability (E). (b) Distributions of observed seizure probabilities averaged in the same way align 457 well with periods of high risk. (c) and (d) show data analogous to (a) and (b) from the self-reported 458 seizures (validation) cohort (N=157). Cyan boundaries depict estimated durations of pro-ictal 459 states, which range from three to five days in the majority of subjects and more than seven days 460 in a minority of subjects. Most subjects whose forecasts did not show IoC reside at the bottom, 461 outside of the cyan boundaries.



463 Figure 4. Hourly forecasts of electrographic seizures. Hourly forecasts were not possible for 464 465 self-reported seizures because time resolution of these data was one day. (a) Distributions of 466 univariate and multivariate hourly forecast performance (at 1-h horizon) guantified as the AUC 467 across subjects. Multivariate models incorporated information from circadian and multidien 468 phases of IEA, as well as the circadian distribution of seizures, yielding AUC with IoC in 18 out of 469 18 (100%) subjects (color dots, p<0.05). (b) AUC as a function of forecasting horizon hours in 470 advance of seizures. (c) As in (a), multivariate models yielded both higher AUC and BSS than 471 univariate models. (d) Phase-space map across 18 subjects showing alignment of critical phases 472 of circadian and multidien cycles with observed seizures (contours represent percentiles), 473 coinciding with times of highest forecasted seizure probability. 474

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#### 477 Online content

- 478 Any methods, additional references, reporting summaries, source data, statements of data 479 availability, and associated accession codes are available in the online version of the paper
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- 480

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## 491 Author contributions

- 492 M.O.B., T.P., V.R.R., and W.T. designed the study. V.R.R. and D.K.S collected the data of the
- development cohort. T.K.T. provided the data of the validation cohort. V.R.R., T.K.T., and M.O.B.
  accessed, selected, and verified the data. T.P., W.T., M.G.L., and M.O.B. performed the analysis.
- 495 T.P., M.O.B., and V.R.R. wrote the manuscript, which all authors edited.
- 496

### 497 **Competing interests**

- 498 M.O.B reports personal fees from Wyss Center for neurotechnology as part-time employee,
- 499 grants from Wyss Center for neurotechnology, outside the submitted work; In addition, Dr.
- 500 Baud has a pending patent under the Patent Cooperation Treaty (#62665486). V.R.R reports
- 501 personal fees from NeuroPace, Inc., outside the submitted work. T.K.T. is an employee of
- 502 NeuroPace, Inc. and receives salary and stock options as compensation. T.P., W.T., M.G.L., and
- 503 D.K.-S. have nothing to disclose.

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