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Prediction of Antiepileptic Drug Treatment Outcomes Using Machine Learning

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Abstract

Objective. Antiepileptic drug (AED) treatments produce inconsistent outcomes, often necessitating patients to go through several drug trials until a successful treatment can be found. This study proposes the use of machine learning techniques to predict epilepsy treatment outcomes of commonly used AEDs. **Approach.** Machine learning algorithms were trained and evaluated using features obtained from intracranial electroencephalogram (iEEG) recordings of the epileptiform discharges observed in Mecp2-deficient mouse model of the Rett Syndrome. Previous work have linked the presence of cross-frequency coupling (*I_{CFC}*) of the delta (2-5 Hz) rhythm with the fast ripple (400-600 Hz) rhythm in epileptiform discharges. Using the *I_{CFC}* to label post-treatment outcomes we compared Support Vector Machines and Random Forest machine learning classifiers for providing likelihood scores of successful treatment outcomes. **Main results.** a) There was heterogeneity in AED treatment outcomes, b) machine learning techniques could be used to rank the efficacy of AEDs by estimating likelihood scores for successful treatment outcome, c) *I_{CFC}* features yielded the most effective *a priori* identification of appropriate AED treatment, and d) both classifiers performed comparably. **Significance.** Machine learning approaches yielded predictions of successful drug treatment outcomes which in turn could reduce the burdens of drug trials and lead to substantial improvements in patient quality of life.

1. INTRODUCTION

EPILEPSY is a major neurological disorder that afflicts approximately 1.8% of the population [1]. Its cause can be attributed to many factors ranging from head trauma to genetic abnormalities. There are more than two dozen commonly used antiepileptic drugs (AEDs), and many more experimental drugs, available to treat the disorder. Determining the most effective treatment for a specific individual often involves a trial-and-error procedure. Furthermore, 20-40% of epileptic patients develop medically refractory (drug resistant) forms of epilepsy [2, 3], though they only become aware of this after having already participated in numerous AED trials.

Antiepileptic drugs can also make the seizures worse and more frequent, and are associated with numerous side-effects that can affect cognition and patients' abilities to perform [4-

6]. Furthermore, patients can build up a tolerance to certain drugs over time [7], at which point the trial-and-error search for a treatment resumes.

Unsuccessful drug trials and delayed treatments highly impact patients' quality of life and are expensive for both patients and the health care system. Determining *a priori* the most effective treatment would go a long way in improving the lives of patients and reducing the financial burden. The first step for developing a successful treatment plan is accurately diagnosing or characterizing the disorder.

In recent years, some progress was made on diagnosing and tracking epileptogenesis for those with medically refractory epilepsy. These studies have provided substantial knowledge on seizure characterization, particularly studies focusing on high frequency oscillations (HFOs). Ripple (80-200 Hz) and fast ripple (>200 Hz) HFOs were found to coincide with seizure episodes [8-10], indicate seizure onset zones [9-11] and vary in intensity corresponding to AED dosages [12]. However, the presence of HFOs alone is not indicative of pathology. Recent work by Guirgis *et al.* highlights that HFO presence is mainly linked to pathology when other rhythms are present, specifically the delta (< 4 Hz) rhythm. Their findings reveal that delta modulation of HFOs emerges at seizure onset and termination, implying that the delta-HFO modulation may be involved in transition mechanisms leading to epileptogenesis [8]. There is an opportunity to further explore the effect of these biomarkers on predicting epilepsy treatment outcome through machine learning methods.

Pharmacological treatment prediction through the use of machine learning methods has previously been applied on major depressive disorders and schizophrenia [13, 14]. The results show that scalp EEG features examining combinations of power, coherence and mutual information measures are effective at predicting favorable treatment response to antidepressant drug therapy. While machine learning techniques have been applied in epilepsy studies to classify seizure events [15], predict the seizure onset [16], and most recently, identify seizure onset zone [17], machine learning methods that predict treatment outcome have not, to the best

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Fig. 1. Characterization of epileptiform discharges in *Mecp2*-deficient mice pre- and post-*mecp2* gene reactivation which were also used for feature extraction and labeling needed for machine learning approaches. A) Time-series recording of typical pre-rescue discharge. B) Frequency decomposition using the EEMD algorithm is able to extract the theta, delta and fast ripple rhythms from the raw iEEG trace. C) Comodulograms showing cross-frequency phase-amplitude coupling prior to *mecp2* gene reactivation shows presence of theta (6-10 Hz) and delta (2-5 Hz) modulation with the fast ripple HFO (400-600 Hz). D) Time-series recording of typical post-rescue discharge. E) Frequency decomposition using the EEMD algorithm shows reduction in fast ripple modulation from the raw iEEG trace post gene reactivation. F) Comodulograms showing cross-frequency phase-amplitude coupling post *mecp2* gene reactivation shows reduction in theta (6-10 Hz) and abolishment of delta (2-5 Hz) modulation with the fast ripple HFO (400-600 Hz).

Fig. 2. Comparison of life spans, durations and phase-amplitude cross-frequency coupling pre and post *mecp2* gene reactivation. A) Lifespan of *Mecp2*-deficient mice is improved post *mecp2* reactivation. B) Occurrences of discharges show a steady increase with age of animals and is significantly reduced post *mecp2* gene reactivation. C) Percentage of discharges exhibiting delta-HFO cross-frequency coupling is significantly reduced post *mecp2* gene reactivation.

1 of our knowledge, been applied in epilepsy research until
2 now.
3
4 In this study we focus on a genetic model of epilepsy, found
5 in Rett Syndrome, which is typically unresponsive to common
6 antiepileptic medication. We show that machine learning
7 (ML) methods that use pre-treatment intracellular
8 electroencephalogram (iEEG) recordings can predict the
9 response to common AEDs.
10
11 Rett syndrome is one of the leading genetic causes of
12 severe mental retardation in females and it has been linked to
13 mutations in the gene encoding methyl-CpG-binding protein
14 2 (MeCP2) [18]. Rett syndrome is characterized by a 6-18
15 month period of normal development, followed by rapid
16 regression of acquired skills leading to a long list of
17 symptoms which includes epileptic seizures [19]. Epileptic
18 seizures are found to occur in 60-80% of Rett syndrome
19 patients and the seizures are typically poorly controlled by
20 classic anti-convulsive drugs [19, 20].
21
22 Although MeCP2 protein is expressed throughout the body,
23 it is relatively more abundant in the brain [21]. The accepted
24 view of MeCP2 function is that it acts to repress genetic
25 transcription through binding of methylated CpG sites and
26 subsequent recruitment of co-repressors. It is also thought that
27 MeCP2 may be necessary for maintenance of mature neurons
28 rather than their development [22].
29
30 Rodent models lacking *mecp2* function have been shown to
31 reproduce many of the behavioral and neurological deficits
32 observed clinically in Rett syndrome patients [23].
33 Recordings of iEEGs from *Mecp2*-deficient mice have
34 revealed spontaneous low frequency oscillations (LFO) in the
35 form of epileptiform discharges in the 6-10 Hz frequency
36 range (Figure 1a,d) [24-26].
37
38 Previous work on female *Mecp2*-deficient mice, building
39 on the findings of the delta-HFO co-modulation showed that
40 the reintroduction of the *mecp2* gene in gene knockout mice
41 results not only in behavioral and physical improvements, but
42 also in the reduction of delta-HFO coupling for discharges
43 greater than 2 seconds in duration (Figure 2) [27].
44
45 This study proposes the use of iEEG-based features to track
46 delta-HFO coupling in *Mecp2*-deficient mice undertaking
47 antiepileptic drug therapy to determine treatment efficacy.
48 Two commonly used machine learning techniques, Support
49 Vector Machines (SVMs) and Random Forests (RF) are
50 trained and evaluated on time-based, normalized power and
51 cross-frequency coupling features to predict the likelihood of
52 treatment outcome for commonly used AEDs.
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2. METHODS

Figure 3 provides an outline of the experimental setup, machine learning methodology including feature extraction, labeling, training and testing used in this study.

2.1 Experimental Setup and Data Acquisition

All animal experimental procedures were approved by local ethics committees in accordance to guidelines of the Canadian Council on Animal Care.

Experimental genotypes were produced by crossing female *Mecp2*^{+/-} mice (*Mecp2*^{tm1.1Bird}, Jackson Laboratory, Bar Harbor, ME) with male wild-type mice described previously [28, 29]. In total there are (n=6) female *Mecp2*^{+/-} subjects. In the case of the gene reactivated model the mice were generated by crossing female *Mecp2*^{+/-} mice with male *Rosa26-Esr/Cre* transgenic mice (*Gt(ROSA)*^{26Sortml(cre/ESR1)Tyj/J}, Jackson Laboratories) [29, 30]. In total there are (n=4) female *mecp2* reactivated mice (rescued mice). All subjects were maintained on a pure C57BL/6 background and housed in a vivarium that was maintained at 22-23°C with a standard 12-hour light cycle commencing at 06:00.

Animals were implanted with stainless steel, polyimide-insulated stainless steel electrodes (125 µm) following procedures described previously [25, 31]. Preconfigured microelectrodes were implanted in the somatosensory cortex (Bregma, -0.8 mm; lateral, 1.8 mm; depth, 1.5 mm) with a reference implanted superficially in the frontal cortex (Bregma +2.8mm; lateral, 1.8 mm; depth, 0.5 mm). iEEG signals were amplified 1000x, bandpass-filtered (0.01 – 1000 Hz) and digitized (Digidata 1300, Axon Instruments, Weatherford, TX, USA). Data were sampled at 60 kHz and stored using Clampfit 10.2 software (Axon Instruments). Recordings sessions lasted from 30 min to 1 h to observe all of the behavior states.

Baseline was taken to indicate *Mecp2*-deficient female mice in the 19-23 months age range. All pharmacological treatments were applied for a period of one day followed by a day of washout. The drugs and dosages used in this study were: Midazolam at 0.5 mg/kg, Ganaxolone at 5 mg/kg, THIP at 5 mg/kg, and Phenytoin at 30mg/kg. All drugs were dissolved in double distilled H₂O and administered intraperitoneally to the animals.

Recordings of iEEG were obtained from *Mecp2*^{+/-} mice exhibiting spontaneous and recurrent epileptiform discharges. These recordings came from pre- and post- *mecp2* gene reactivation, and pre- and post- anti-epileptic drug (AED) treatment regimens (Figure 3a). Epileptiform events were identified in the recordings using an automated detection technique based on predefined selection criterion as described previously [24, 32]. Data preprocessing consisted of downsampling to 4k Hz followed by removal of 60 Hz line noise using a high order FIR notch filter with +/- 0.5 Hz cutoffs. Segments with large amplitude muscle artifacts were excluded from analysis.

2.2 Features for Machine Learning

In this study we investigate power-based features from the normalized complex wavelet transform (CWT), cross-frequency coupling based comodulogram, and time-based features from extracted rhythms using ensemble empirical mode decomposition (EEMDs) (Figure 3b). Two machine learning algorithms: SVMs and RFs were evaluated on their ability to predict treatment outcome from iEEG-based features (Figure 3c).

A

B

C

Fig. 3. Overview of experimental design, signal processing and machine learning methods and their interconnection. A) Experimental setup consisted of pre and post gene reactivation along with pharmacological testing. B) Signal processing overview highlights the rhythm extraction using complex CWT and extraction of specific rhythms of interest using EEMD for purposes of generating labels. C) Machine learning overview highlighting the selection of machine learning algorithms using t-SNE projections.

2.2.1 Comodulogram

Time-frequency power distributions were obtained by applying a continuous wavelet transform (CWT) on iEEG time-series recordings $x(\hat{t})$, where $\hat{t}$ is a time interval centered on an epileptiform discharge. The CWT measures the correlation between a signal $x(\hat{t})$, and a wavelet basis, ψ , for different scales, s , and time shifts τ [33] and is defined as,

$$W(s, \tau) = \int_{\hat{t}} x(t) \psi_{s,t}^*(t) dt \quad (1.1)$$

where,

$$\psi_{s,t}^*(t) = \frac{1}{\sqrt{s}} \psi_o\left(\frac{t-\tau}{s}\right) \quad (1.2)$$

is the basis function with * denoting the complex conjugate. The basis function used here is the complex Morlet wavelet defined according to the following form,

$$\psi_o(t) = \frac{1}{\sqrt{2\pi}} \exp\left(i\omega_c t - \frac{t^2}{2}\right) \quad (1.3)$$

The scales were transformed to appropriate frequencies f , from the angular frequency ω_c , using the relation $\omega_c = 2\pi f s = 5.1 \text{ rad/s}$. The result of the CWT yielded complex valued coefficient matrix,

$$W(f, t) = w(f, t) + i\tilde{w}(f, t) \quad (2.1)$$

for which the magnitude was obtained as a measure of power over time and frequency. The rows corresponded to frequencies 1 to 600 Hz by 1 Hz step size, and the columns corresponding to the duration of the recording $x(\hat{t})$.

To visualize the high and low frequencies on the same scale, the time-frequency vectors were further z-score normalized according to the following,

$$W_{norm}(f, t) = \frac{|W(f, t) - \mu(f)|_{t_1}^{t_2}}{\sigma(f)|_{t_1}^{t_2}} \quad (2.2)$$

where variables μ and σ represent the mean and standard deviation from wavelet coefficient magnitudes for each corresponding frequency taken from a two second baseline segment $\hat{b}$ obtained prior to seizure onset (i.e. $\hat{b} \in [t_1, t_2]$).

Equation 2.2 yields the power-based feature. Normalized CWT power features were obtained for the time windows spanning the duration of the discharges. Power features were obtained by averaging CWT coefficients across time for each frequency band (i.e. $\langle W(f, \hat{t}) \rangle$) from 1 to 600 Hz resulting in a 600 point feature vector.

Cross-frequency coupling for a time interval $\hat{t}$, is proposed as a composite complex-values signal $S_{CFC}(\hat{t})$ consisting of an amplitude time-series of one higher frequency $A(\hat{t}, f_H)$ with a lower frequency of phase time-series $\varphi(\hat{t}, f_L)$ as shown,

$$S_{CFC}(\hat{t}, f_H, f_L) = A(\hat{t}, f_H) e^{j\varphi(\hat{t}, f_L)} \quad (3.1)$$

The time-series of the amplitude envelope $A(\hat{t}, f_H)$ and instantaneous phase $\varphi(\hat{t}, f_L)$ were determined from the respective complex wavelet coefficients,

$$A(\hat{t}, f_H) = |w(\hat{t}, f_H) + j\tilde{w}(\hat{t}, f_H)| \quad (3.2)$$

$$\varphi(\hat{t}, f_L) = \arctan \frac{\tilde{w}(\hat{t}, f_L)}{w(\hat{t}, f_L)} \quad (3.3)$$

The coupling of the amplitude of a higher frequency signal, $A(\hat{t}, f_H)$ for a phase of a lower frequency signal $\varphi(\hat{t}, f_L)$ was assessed over a range of frequency pairs using the algorithm proposed by Tort *et al.* [34]. The $\varphi(\hat{t}, f_L)$ signal was segmented into 20 degree intervals resulting in $N = 18$ bins. Within each bin the amplitude envelopes were averaged $\langle A(\hat{t}, f_H) \rangle$. The mean amplitude was normalized by the sum over all mean amplitudes in each phase bin, according to,

$$p_j(\hat{t}, f_H, f_L) = \frac{\langle A(\hat{t}, f_H) \rangle_j}{\sum_{k=1}^N \langle A(\hat{t}, f_H) \rangle_k} \quad (4.1)$$

producing a probability density value p_j , where j indicates the phase bin number which is associated with f_L . Then an entropy measure defined by:

$$H(\hat{t}, f_H, f_L) = -\sum_{j=1}^N p_j(\hat{t}, f_H, f_L) \log(p_j(\hat{t}, f_H, f_L)) \quad (4.2)$$

was determined and normalized to obtain the index of cross-frequency coupling,

$$I_{CFC}(\hat{t}, f_H, f_L) = \frac{H_{max} - H(\hat{t}, f_H, f_L)}{H_{max}} \quad (4.3)$$

where H_{max} is the maximum possible entropy value, which for a uniform distribution has a value $H_{max} = \log N$.

The I_{CFC} measure described by equation 4.3 when examined over a range of frequencies results in the comodulogram.

Phase-amplitude cross-frequency coupling features were obtained using a comodulogram applied over a 2 second time window centered on the discharge event. The f_L spanned 2 - 12 Hz, and the f_H spanned 80 - 600 Hz. This resulted in a large feature vector which needed to be compressed vertically to remain similar in size to the other feature sets. The initial feature vector, which had a dimension of 11 by 520, was compressed vertically to 11 by 30, yielding 330 pixel-based features of the phase-amplitude cross-frequency coupling.

2.2.2 EEMD Rhythm Extraction

The Ensemble Empirical Mode Decomposition (EEMD)

Fig. 4. Low dimensional representation of machine learning features using t-SNE. Each animal subject was identified by a different color. A) EEMD time-based features showed clustering B) Wavelet-based normalized power features were scrambled with little to no clustering reducing possibility for separability of samples C) Comodulogram-based features of phase-amplitude cross-frequency coupling show reasonable clustering D) Concatenating EEMD time-based and comodulogram features showed distinct clustering and strong separability making it the preferred feature set.

was applied to extract the LFO and HFO rhythms [35]. EEMD is applied to decompose signals into rhythms and it does not require *a priori* knowledge of the frequency ranges of the rhythms, as would have been needed for bandpass filtering. Furthermore, EEMD is better suited for extracting rhythms with time-varying frequencies that span large frequency bands.

The EEMD separates a signal into multiple rhythms referred to as intrinsic mode functions (IMFs). The decomposition is adaptive and dependent on local time characteristics of the data. In our approach the noise variance σ^2 was set to 0.2, and the number of iterations was set to 100, resulted in 9 IMFs. The IMFs spanned over a large range of frequencies with IMF1 representing the highest and IMF9 being the lowest frequency rhythm. The theta rhythm LFOs (6-10 Hz frequency range) were obtained from IMF 8, the delta LFOs (2-5 Hz frequency range) were obtained by combining IMF8 and IMF9 and the fast ripple HFOs (400 - 600 Hz frequency range) were obtained from the IMF2.

EEMD time-based features were computed for each IMF over time windows $\hat{t}$, spanning the duration of the discharges. The features selected have previously been used in epilepsy studies using machine learning and are formed from a combination of power, RMS power, mean, variance,

skewness, kurtosis, line length, zero crossings, non-linear energy, activity, mobility and complexity [36] resulting in an 81 feature vector.

2.3 Machine Learning Algorithms

Feature sets were z-score normalized over all samples to reduce the effect of feature scale during training. A two dimensional representation of the features was obtained using t-Distributed Stochastic Neighbor Embedding (t-SNE). The 2-dimensional projections were identified by the subject they came from (Figure 4) and by their response to the AED treatments (Figure 5). The level of separability suggests the viability of Support Vector Machines (SVMs) and Random Forest (RF) machine learning classifiers for predicting the treatment outcomes [37].

2.3.1 Support Vector Machines

SVMs with Gaussian kernels, implemented in the LibSVM library [38], were trained to predict treatment outcomes for several AEDs. SVMs were chosen for their suitability to small data sets with large feature vectors. SVM work by applying a n-dimensional transformation to construct a hyperplane that maximizes the separation margin between input data classes [39].

Training consisted of 5-fold cross-validation to select the best regularization parameter C and the Gaussian parameter γ . An exponential grid search over the parameters C (2^{-3} , 2^{-4} , ..., 2^{10}) and γ (2^{-18} , 2^{-17} , ..., 2^{-3}) was then performed. The parameter pair yielding maximum performance on the training set was selected for testing.

2.3.2 Random Forest

RF classifier, proposed initially by Breiman [40], was used as one of the predictive models for AED treatment outcome. The RF is made up of individual classification trees. Each tree independently able to make classification decisions. During training a subset of the trees are randomly selected and trained on the dataset. The core of the random forest classifier is the binary decision tree, a data type that stores elements hierarchically in nodes. Each decisions tree is grown on different bootstrapped sample collections (i.e. randomly drawn instances with replacement from the original dataset) on a randomly selected subset of all available predictors. The random selection of predictors increases the generalizability of the individual decisions trees, whereas the collection of multiple decision trees in one forest increases model performance. As a result RFs are well suited to nonlinear, high dimensional feature spaces, and provide a good comparison to SVMs. Furthermore RFs generally work out of the box with minimal parameter searching.

Random Forest (RF) implementation followed similarly to the SVM implementation with less parameter searching. A search over the number of trees was performed from 50 to 400. As it was observed that after 100 trees the performance did not improve, the number of trees was fixed at 100 for the remainder of the testing.

2.4 Training

Typical machine learning approaches would warrant some form of feature selection, such as the minimal-redundancy-maximal relevance criterion (mRMR)[41]. In this study we maintained feature independence to investigate the contributions of each feature type.

In total there were 263 unique discharges distributed across six subjects along with four feature vectors for each sample. The feature vectors were combined with samples to yield three unique feature matrices (samples x features) representing the EEMD time-based features, (263x81), normalized CWT power feature, (263x600), and comodulogram features, (263x330). An additional feature set was obtained by joining the EEMD time-based features with the comodulogram features to yield a fourth feature matrix (263x411). This was done to see if the combination of the comodulogram features with the EEMD time-based features would yield any improvements in prediction accuracy.

To maintain independence of training and testing sets, the training sets for each AED were confined to two subjects, one a responder and the other a non-responder. Only half of the available samples were selected for training and equal number of samples from the two classes were used for testing.

	Percentage of Discharges with Delta - HFO Coupling						Avg.
BASLINE	50	67	40	60	100	44	60
MID	0	54	0	100	100	0	42
GAN	33	69	100	38	0	35	46
THP	54	65	0	57	0	25	33
PHE	100	0	100	100	100	25	71

Table 1. Examination of delta-HFO phase-amplitude coupling pre and post antiepileptic drug administration. Where pre is taken to be the baseline.

2.4.1 Labeling of Responders and Non-Responders

Responses to AED treatments were determined from post-treatment iEEG recordings by examining the percentage of long duration discharges exhibiting delta-HFO cross-frequency coupling (Table 1) as measured by I_{CFC} .

In order to determine the significance of the I_{CFC} values, we chose to use a method known as bootstrapping. In such a method, many time-series signals, referred to as surrogates, are generated from the original data to test the null hypothesis that the observed I_{CFC} resulted by chance. The hypothesis was tested by randomizing the phases across frequency components of the surrogate signals, while keeping all other statistical properties of the signal constant, and obtaining their I_{CFC} . If the I_{CFC} obtained on the original signal is found to be significantly larger than the distribution of I_{CFC} values generated from the ensemble of surrogate signals, then one can be confident to reject the hypothesis.

Surrogate time-series signals were generated by employing amplitude adjusted Fourier transform (AAFT) as described by Theiler et al. [42] which generates a vector of random numbers following the Gaussian distribution which are then rank-ordered according to the same rank-order of the original time-series signal. The fast Fourier transform (FFT) was then applied to the IMFs extracted from the iEEG signal $x(\hat{t})$ using EEMD and each phase was multiplied by $e^{j\vartheta}$, where ϑ is a random number from a uniform distribution between $[0, 2\pi]$ and $\vartheta(f) = -\vartheta(-f)$. This allowed for the inverse FFT to be a vector of only real values. The resulting real-only inverse FFT output yielded the surrogate time-series.

The I_{CFC} computation was performed on surrogate IMFs using Hilbert transform to obtain $A(\hat{t}, f_H)$ and $\varphi(\hat{t}, f_L)$. The significance of the phase-amplitude couplings were determined from $N = 200$ surrogate time-series samples comparing to see if the I_{CFC} obtained from the original undistorted signal exceeded the 95% percentile of the I_{CFC} values obtained from surrogate cases.

2.4.2 Testing

Performance was evaluated for sensitivity and specificity by performing a Receiver Operating Characteristic (ROC) on the predicted probability scores[43, 44]. The area under the ROC curve provided a score to quantify the performance. Predictions were further evaluated on an individual basis by counting the number of samples predicting successful treatment outcome over the total number of samples, yielding a likelihood score for treatment efficacy.

Fig. 5. Low dimensional feature projections for the antiepileptic drug THIP (one of four tested) shows non-responders in red and responders in cyan. A) EEMD time-based features required a nonlinear separation, B) Normalized power features showed no separability, C) Comodulograms are linearly separable with minor overlapping errors, and D) Feature set representing the concatenation of EEMD time-based and comodulogram features achieves the most linear separation of responders and non-responders.

3 RESULTS

3.1 Pathology linked to delta – HFO Coupling

The genetically modified, *Mecp2*-deficient mouse model of Rett Syndrome shows presence of epileptiform discharges (Figure 1a). This genetic model provides a means to evaluate iEEG features pre- and post- *mecp2* gene reactivation (pre-rescue), and provides a means of identifying the link to pathology. EEMD and comodulograms analyses of pre-rescue discharges highlight the presence of delta (2-5 Hz), theta (6-10 Hz) and fast ripple (400-600 Hz) rhythms with the fast ripple rhythms modulated by the phase of the delta and theta rhythms (Figure 1b, 1c).

Comodulograms generated on typical post-rescue discharges (Figure 1d) reveal that delta (2-5 Hz) modulated fast ripple (400-600 Hz) HFO presence is abolished, whereas theta (6-10 Hz) modulated fast ripple HFO is still present in a diminished form after gene reactivation (Figure 1e, 1f). Reactivation of the *mecp2* gene increased the lifespan of *Mecp2*-deficient mice, thus correcting the effects of the pathology (Figure 2a). Recordings of iEEG in *Mecp2*-deficient mice show a progressive increase in discharge occurrence with age, which is reduced post *mecp2* gene

reactivation as shown in Figure 2b. The percentage of discharges with significant delta-HFO modulation is also shown to increase with age and is reduced in post-rescue mice (Figure 2c).

Previous studies show that these rescued mice perform better on physical and cognitive tests, and have improved life spans that come close to the longer lifespans observed in wild types [30] (figure 2a). These results provide strong evidence that the presence of long duration discharges with delta-fast ripple modulation (delta-HFO) are indicators of pathological seizure activity. This suggests that the extent of delta-HFO modulation could be used to score post treatment outcome [45].

3.2 AED Treatment outcomes varied across subjects

Delta and fast ripple rhythms were extracted using EEMD to quantify the extent of delta-HFO phase-amplitude coupling in 6 *Mecp2*-deficient mice. Prior to AED treatment there was an elevated presence of delta-HFO coupling in the long duration discharges (60% +/- 9%), as shown in Table 1. Post AED treatments it was observed that Midazolam, Ganaxolone, THIP showed on average a decrease in delta-HFO modulation, whereas Phenytoin showed an increase in delta-HFO modulation.

Fig. 6. ROC evaluation of SVM and RF machine learning methodologies across the four feature sets for predicting treatment efficacy for THIP antiepileptic drug. In all cases the normalized power features performed inferior to other features. EEMD time-based achieved reasonable performance and comodulograms features achieved the best results. The combined EEMD time-based and comodulogram feature vector achieved a marginal improvement on the comodulogram results.

Examining the delta-HFO modulation in long duration discharges on a per subject basis revealed high variability in treatment outcome. For example, while half of the subjects were effectively treated with Midazolam, the other half either became worse or showed little to no change. A similar finding was observed for the other three AEDs, highlighting that treatment outcome is highly dependent on the individual subject.

3.3 Combined features provide greatest class separation

T-SNE low dimensional projections of EEMD time-based, normalized power and phase-amplitude coupling (comodulogram) features are shown in Figure 4. Samples are colored according to which subjects they came from. The projections revealed that selection of features is vital in achieving class separation and thus has a profound effect on determining treatment outcome.

The normalized power feature projections did not show any clustering by individual animal subjects and were the least useful features in terms of separating responders and non-responders (Figure 4b). The EEMD time-based and comodulogram features achieved the best separability with distinct clusters for each of the animal subjects. The comodulogram showed less pronounced clustering when compared to the EEMD time-based features, however, certain mouse subjects were better defined.

The best results were achieved when both EEMD time-based and comodulogram features were used. This was further validated when the labels were changed from mouse subjects to responders and non-responders. Figure 5 compares responders and non-responders to THIP and it can be seen that EEMD time-based features would lead to non-linear separation requirements which would pose a greater challenge to applying machine learning techniques for prediction. Overall the EEMD time-based and Comodulogram combination produced the best class separation.

3.4 iEEG-based features predict treatment efficacy

To determine whether it is possible to determine treatment outcome from the iEEG, we examined different combinations of features and machine learning algorithms. A sample result of sensitivity versus specificity is shown for the THP training case (Figure 6). The ROCs show similar performance with the SVMs and Random Forests, with the SVMs performing marginally better. The greatest variability in success came from the features selected. In all cases the normalized power features performed poorly, followed next by the time-series features which showed varied success across different drugs. The most consistent performance came from the combined EEMD time-based and comodulogram data sets, reaching accuracy levels of 97.6%.

The results summarizing the combined time-series and comodulogram features trained with SVMs and RFs are shown in Figure 7. The figure shows the percentage of discharges that are correctly identified over all the discharges tested. A higher percentage indicates that the treatment was predicted to be more effective and likely to lead to a favorable outcome. The green and brown bars (responder and non-responder respectively) indicate the actual outcome for the specific drug. The results for the SVM based predictions (Figure 7a) correlate closely to the treatment outcomes percentages shown in Table 1. Furthermore, in many cases the predicted results matched the uncertainty in treatment efficacy. For example, in Figure 7a, mouse 2 was predicted to have a 67% likelihood of effective treatment outcome to Midazolam. This matches closely to the expected delta-HFO outcome score of 54% seen in Table 1. Even though Midazolam was not effective on mouse 2, it was not completely terrible either. The RF based predictions (Figure 7b) also performed well overall, but there are a couple instances where the prediction was completely wrong. For example, the predictions of outcome for the Ganaxolone drug for mouse 2 showed a 100% success rate, which we know was not successful. Aside from some misclassifications, RF performed similarly to SVM, and in some cases it was slightly better.

Overall, the SVMs were the machine learning method of choice. The predicted likelihood scores obtained with SVMs aligned well with the expected labels and there were no obvious misclassifications.

4 DISCUSSION

4.1 iEEG-based features predict epilepsy treatment outcome

Patient variability is a serious challenge to selecting treatments for epilepsy. Often antiepileptic drug treatments are cycled through until an effective treatment can be found, and with over two dozen commonly prescribed AEDs available, it can be a cumbersome process. There are certain AEDs that have been found to be statistically more likely to lead to a successful treatment outcome and it is those AEDs that typically are tried first. However, the likelihood of a

Fig. 7. Predicted likelihood of favorable treatment outcome across four commonly used AEDs using SVM and RF machine learning algorithms. Green bars indicate patient was successfully treated by specific AED, and brown bars indicate unsuccessful treatment. A) SVMs predictions accurately predicted treatment outcome for all AEDs. B) RFs had comparable prediction results, with misclassifications for Ganaxolone treatment for mice 2 and 4 and Phenytoin for mice 1.

successful treatment reduces with each round of AED application [46], possibly due to patient desensitization to AEDs which happens over time.

Our findings reveal that iEEG-based features, obtained from the subject, can be used to predict treatment outcome to anti-epileptic drugs (AEDs). By indicating which patients would be unresponsive to certain AEDs it would avoid unnecessary testing and would have a profound effect on patient quality of life.

Approximately 20-40% of the patients are unresponsive to AED treatment [2, 3], which is a diagnosis that can only be ascertained after an exhaustive search over many AEDs. This is particularly evident in cases of Rett Syndrome where patients generally do not respond favorably to commonly prescribed AEDs [19, 20]. In these hard to treat cases, it would be beneficial to pre-identify the most likely AED for each subject based on their biomarkers rather than general population statistics.

4.2 Critical LFO-HFO Ranges for Tracking Efficacy of Therapies

In recent years there has been extensive research on detection of seizure pathology through the use of biomarkers based on time-frequency power distributions [9], phase – phase coupling [10] and phase-amplitude coupling [8]. In particular, Guirgis et al., showed the presence of delta-HFO to be a marker for epileptogenesis [8].

Interactions between theta and gamma frequency ranges have frequently been identified with memory coding [47, 48] and cognitive processing during performance task [34]. These cognitive links suggest that high levels of CFC is not pathological on its own, but rather the specific frequencies of interactions that are linked to the pathology. In the case of memory coding, it has been shown that even under error trials, where presumably there is miscoding of information, there is still a measured elevation of the CFC index [34].

The results presented here further support the importance of the interactions of the rhythms. Specifically the interactions between the delta and HFO frequency ranges [27] are distinct from theta and HFO frequency ranges (Figure 1c, f), for tracking improvements in lifespan longevity (Figure 2).

4.3 Comodulogram as a critical feature for prediction

Our findings show that variants of the above reported biomarkers can also be used as features to predict treatment outcome of AEDs. When comparing features across individual mice using t-SNE it was noted that EEMD time-based and comodulogram features produced distinct clusters with minor overlapping across other mouse clusters (Figure 4). This suggests that such features managed to extract some latent information related to subject variability. On the other hand, power based features showed no discernable clusters, which was evident in their poor performance in testing. This could be due to the short duration of the fast ripple activity which could have been averaged out over the time window.

Evaluation of three features using ROCs for both SVMs and RFs (Figure 6) showed that comodulogram features

(AUC 0.974) outperformed those of EEMD time-based (AUC 0.918) and normalized power (AUC 0.745).

4.4 Comparison of Machine Learning Algorithms

On average SVMs and RFs performed equally well on the ROC evaluations. However when the techniques were evaluated to predict treatment outcome of four different AEDs, SVMs were found to predict the treatment outcome of outliers found in RF predictions. For example, in Figure 7, RF predictions of treatment outcome for Ganaxolone applied on mouse 2 was close to 100%, when it should have been closer to 0%, whereas SVMs predicted 44%. Similarly, for Phenytoin the prediction for mouse 1 was 84% when it should have been closer to 0%, whereas SVMs predicted 59%. Generally, SVMs estimated 90% or greater likelihood scores only for successful treatments.

When the t-SNE projections were examined in terms of responders and non-responders, two classes were well clustered and separable. The EEMD time-based features typically yielded a non-linear separation between responders and non-responders, whereas comodulogram were linearly separable. This may explain why the RFs, which are ideally suited for non-linearly separable classifications, seemed to do better than SVMs on EEG time-based classifications.

5 CONCLUSION

The focus of this work was to investigate iEEG-based features, first as biomarkers of epilepsy in a Mecp2-deficient mouse model of Rett Syndrome, and second, as predictors of treatment outcome to AEDs. Specifically, cross-frequency coupling features, in combination with EEMD time-based features, yielded the best likelihood scores of treatment outcome in a machine learning framework. The work presented here may one day lead to more efficient selection of antiepileptic drug treatments from biomarkers obtained from patients, leading to a customized treatment that could lead to more effective treatment outcomes. These techniques are scalable, hence could be extended to treatments focusing on diet, surgery and neuromodulation [49], which could help epileptologists in choosing the most appropriate therapy for their patients.

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