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Use of Machine Learning for Predicting Levetiracetam Treatment outcome in Temporal Lobe Epilepsy.

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Abstract

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Abbreviations: ASMs = Anti-seizure medications; AUC = area under the curve; CV = cross-validation; EEG = Electroencephalogram; LEV = Levetiracetam; NSF = non-seizure free; PCA = Principal Component Analysis; PLS = Partial Least Square; ROC = Receiver Operating Characteristic; SF = seizure-free; T0-EEG = EEG performed before LEV initiation; T1-EEG = EEG performed after 3 months of LEV initiation; TLE = temporal lobe epilepsy.

Highlights:

1. We provide a proof-of-concept pipeline for predicting the clinical response to anti-seizure medications in people with epilepsy.

2. Quantitative EEG modifications induced by Levetiracetam are predictive of seizure-freedom in patients with Temporal Lobe Epilepsy.

3. Machine-learning approaches using EEG signals will help to develop personalized models for anti-seizure treatment selection.

1. Introduction

Epilepsy is a worldwide serious neurological condition, accounting for 1% of the global burden of disease (Murray et al. 1994), and Temporal Lobe Epilepsy (TLE) is the most common cause of drug-resistant epilepsy in the adult population (Engel et al. 2012). For these patients, the electroencephalogram (EEG) is a pivotal neurophysiological technique in both confirming diagnosis and guiding clinical management (Koutroumanidis et al. 2017). Quantitative analysis of the EEG with the aim of documenting the effect of specific drugs in the electrical activity of the brain is known as pharmaco-EEG (Höller et al. 2018; Pellegrino et al. 2018; Ricci et al. 2021).

The analysis and the interpretation of EEG brain activity recordings can be considered as a multivariate problem in which a trade-off between the large dimensionality of the data and the limited number of participants must be considered (Van Niel et al. 2005; Assenza and Di Lazzaro 2015; Liu and Gillies 2016). This problem leads to often consider a-priori assumptions on temporal, spectral and spatial characteristics of the signal of interest. With this approach, characteristic features can be extracted by averaging among multiple channels, multiple time instants or multiple frequencies. However, important information may be lost in the averaging process (Bishop 2006). An alternative or complementary method to feature extraction are machine learning approaches (Bishop 2006). Once the machine learning model is trained and validated, the resultant associated weights can be interpreted to recognize relevant features extracted by the model itself and how they are related to the specific outcome. Moreover, data-driven methods allow to use the cross validated model for inference on new data at a single subject level and can be updated once the outcome is known (i.e. seizure freedom after anti-seizure medication [ASM] initiation).

Since no definite EEG prognostic biomarkers for ASMs efficacy have been defined yet (Ricci et al. 2021) and since the EEG is one of the most important diagnostic techniques in patients with epilepsy, it would be straightforward to incorporate machine-learning EEG studies in the initial administration of ASMs in patients with epilepsy, in order to estimate the predictability of treatment response. Such

an approach has the potential to allow for the development of a clinical decision-making tool for data driven, personalized ASMs treatment selection for people with epilepsy.

The goal of this study is to determine the predictive power for seizure-freedom of 19-channels scalp EEG in a population of newly diagnosed TLE patients using a machine-learning approach. We hypothesize that the modifications in EEG activity induced by an ASM can predict long-term clinical outcome (i.e. seizure freedom after two years of therapy). To test our hypothesis: (i) we performed quantitative EEG analysis on a population of TLE patients, before and after 3 months the initiation of Levetiracetam (LEV) therapy; (ii) compared the EEG modifications induced by LEV between seizure-free (SF) and non-seizure-free (NSF) patients; and (iv) tested whether such modifications predicted outcome in an optimized and cross-validated framework using a machine-learning approach.

2. Methods

2.1 Subjects and Data Collection

We retrospectively reviewed the data of twenty-three newly diagnosed TLE patients enrolled at the epilepsy clinic of Department of Human Neurosciences of Policlinico Umberto I University Hospital of Rome and of Campus Bio-Medico University of Rome between January 2016 and March 2018. Patients were included if they met the following inclusion criteria: (i) had a clinical diagnosis of TLE and > 18 years old; (ii) had at least two EEG recordings occurring immediately before (i.e. < 30 days) LEV assumption and after 3 months of LEV initiation; (iii) had at least 5 minutes of resting state EEGs free of relevant artifact; (iv) their two-years post medication follow-up was available from their medical records. The exclusion criteria were: (i) TLE patients taking neuroactive drugs other than ASMs; (ii) Clinical seizure/s in the 24 hours before the EEGs; (iii) TLE patients with one EEG recording containing more than 20% of interictal epileptic activity. The study protocol received approval by the ethic committee of Policlinico Umberto I Ethic Board-Rome- and Campus Biomedico

University Ethic Board-Rome, which waived the need for written informed consent due to the study retrospective character. All procedures were performed in agreement with the 1964 Helsinki declaration and its later amendments.

2.2 EEG recording

Nineteen channel-EEG was acquired with a Micromed recorder (Micromed, Mogliano Veneto, IT). The electrodes were placed according to the international 10-20 system (Fp1, Fp2, F3, F4, C3, C4, P3, P4, F7, F8, T3, T4, T5, T6, O1, O2, Fz, Cz, Pz). The reference was placed on FPz and the ground on FCz . Impedance was kept below 5 kOhm for all electrodes. The sampling rate was set to 256 Hz. The resting EEG recording lasted 15 minutes and was performed with closed eyes, with patients seated in a comfortable armchair in a quiet room. All the EEGs were performed always using the same apparatus.

2.3 EEG analysis

Quantitative EEG analysis was performed using the Brainstorm Toolbox for Matlab (Tadel et al. 2011) and in home Matlab code for Partial Least Square (PLS) analysis. Offline data pre-processing was performed using Brainstorm and included: (i) visual inspection for rejection of possible interictal and ictal epileptiform activity; (ii) 50-Hz notch filter; (iii) bandpass filter between 1 and 70 Hz (linear phase finite impulse response filter); (iv) EEG re-reference to average; (vi) correction for pulse and eye-blink artifacts using an automated Independent Component Analysis procedure (Barbati et al. 2004; Croce et al. 2018; Ricci et al. 2020). Epochs containing interictal activity (spikes, spike and wave complexes, sharp waves) were manually rejected by three experienced neurophysiologists blind to the clinical data (LR, PP, and MT). We selected a total of 300 ± 75 s seconds continuous epochs from the original resting state EEG, free from relevant artifacts and epileptiform activities, for further analysis (Babiloni et al. 2020). As measure of activity, we computed the Effective Power for the

following frequency bands: (i) Delta δ: 2-4 Hz; (ii) Theta θ: 5-7 Hz; (iii) Alpha α: 8-12 Hz; and (iv) Beta β: 13-20 Hz. Specifically, EEG signals were band-pass forward-backward filtered in each of the above defined frequency bands by means of a zero-phase Butterworth filter and standard deviation of the signal calculated.

2.4 Definition of Clinical Outcome

To assess whether pharmaco-EEG analysis of LEV was able to predict the individual patient's outcome, we used a Machine-Learning based approach on the early effective power modification induced by LEV in our cohort of newly diagnosed TLE patients. We considered seizure-freedom after at least two years following the introduction of LEV to be the ground truth, i.e. unambiguous proof of LEV efficacy. Seizure freedom was defined as absence of seizures or auras for at least the previous two years on unchanged medications (Stephen and Brodie 2002) based on patient self-reporting and clinical diary.

2.5 Machine-Learning analysis

Due to volume conduction effects, the correlation between both channels and frequencies of EEG recordings is high (van den Broek et al. 1998). Such collinearity coupled with the large numerosity of features with respect to samples (i.e. subjects) may corrupt the prediction of an output based on multichannel recordings and may make the prediction prone to overfitting and poor generalization (Magidson 2013). Different linear and nonlinear regression and classification algorithms have been developed to address the overfitting problem (Huopaniemi et al. 2009; Kolter and Ng 2009). In this work, the Partial Least Square (PLS) analysis (i.e. a linear regression analysis employing a space dimension reduction) was used (Wold et al. 1984; Abdi and Williams 2013). The known linear properties of the generation of the EEG recordings from intracortical electric currents justifies the choice of a linear analysis procedure (Hallez et al. 2007). The PLS was used to predict the therapy

effect from EEG recordings. Indeed, PLS has been proven to be highly effective in reducing overfitting in the presence of highly correlated features. The underlying assumption of PLS is that the observed data is generated by a system or process which is driven by a small number not directly observed or measured variables (latent variables). With the PLS is possible to identify components that capture most of the information in the independent variables (e.g. linear combinations of EEG channels and frequency band powers) and that are meaningful for the prediction of the dependent variable (i.e. sustained seizure freedom after ASM initiation). This happens reducing the dimensionality of the regression problem by using fewer components than the original number of independent variables. Considering the PLS as a supervised learning version of the Principal Component Analysis (PCA), the difference between PCA and PLS is that PCA reduces the dimensionality of the feature space by considering the eigen solutions of the space covariance matrix, whereas PLS calculates the feature space component by maximizing the covariance among the independent and dependent variables (Barlow 1989; Jolliffe and Cadima 2016). The pipeline of our analysis is summarized in Figure 1. The EEG effective power in 4 frequency bands (δ, θ, α and β) and in the 19 channels for T0 (the EEG performed before LEV initiation) and T1 (the EEG performed after 3 months of LEV initiation) were considered as independent variables for a total of 152 features whereas the dependent variable was the Clinical Outcome. The PLS algorithm needs a-priori choice of one parameter: the number of uncorrelated components (K) to be used for regression. Hyperparameter optimization is usually performed through a training, a validation and a test set. The training set is used to train the algorithm (e.g. estimate PLS weights), the validation set is used to optimize the hyperparameter (e.g. estimate the optimal K) and the test set is used to evaluate the generalization performance of the learning process. This separation of data implies a reduced sample numerosity in a trade-off choice among sets (Kearns and Ron 1999).

Another approach that allows to minimize the loss of samples in the different sets, while evaluating the algorithm generalization capabilities, is cross-validation (CV). In the CV framework, data are

divided in folds and the model is trained on all data except one-fold in an iterative manner. The out-of-sample performance (i.e. generalization) is assessed based on the remaining fold and averaged across iterations. If the number of folds equals the number of samples (one-fold per sample) the procedure is defined leave-one-out CV (Filzmoser et al. 2009). CV can be adapted for simultaneous selection of the best set of hyperparameters and for generalizable error estimation through a procedure defined nested CV (nCV) (Krstajic et al. 2014). Starting from k folds, nCV is performed based on an outer loop of k folds and an inner loop of k-l folds. Whereas the outer loop estimates the generalization performances of the model (i.e. test), the inner loop evaluates the optimal hyperparameters (i.e. validation). In this work, a leave-one-out nCV was implemented to assess the PLS generalization performance and optimal number of components.

2.6 Statistical analysis

Classification performances of the PLS were assessed through Receiver Operating Characteristic (ROC) analyses considering the out-of-training-sample (i.e. inferred response) treatment response to therapy. Patients who responded to therapy (sustained seizure freedom after two years of therapy) were attributed to the "negative" group, whereas patient showing a non-major pathological response (non-seizure free) were attributed to the "positive" group. The ROC analyses were also performed on random shuffled outcomes to simulate the null hypothesis and evaluate its confidence interval (repeated 1000 times). The ROC analysis delivered an Area Under the Curve (AUC) which, using the random shuffled outcomes, could be transformed into a z-score for assessing its statistical significance. Patients' clinical characteristics were compared between seizure-free (SF) and non seizure-free (NSF) patients using the χ^2 test for categorical variables and Mann-Whitney U tests for continuous variables. Significance level was set at $p < 0.05$. Results are reported as mean ± standard deviation unless differently stated. The Statistical Analysis was performed in Matlab (The MathWorks Inc. Natick, Massachusetts, US).

3. Results

3.1 Patients clinical characteristics

Twenty-three patients with TLE (13 females) satisfied all the inclusion and exclusion criteria and were included in this study. Clinical and demographic characteristics of our cohort are reported in Table 1. Twenty patients (86.9%) experienced a >50% seizures reduction, of whom twelve (52.5%) achieved seizure-freedom after the introduction of LEV. The mean age at the time of LEV introduction was 50±22.3 years (range: 20-86 years). Eleven patients (47.8%) had an abnormal MRI with different diagnoses (see Table 1) as cause of their epilepsy, without association with clinical outcome after LEV therapy (p=0.54). The mean LEV maintenance daily dose was 1250±391.7 mg (range: 1000-2000 mg). Five patients (21.7%) experienced non-serious adverse events related to LEV therapy.

3.2 Prognostic value of EEG analysis using PLS

A total of 152 features were extracted from the EEG recordings calculating the effective power for each channel and for four frequency bands (delta: δ, theta: θ, alpha: α and beta: β) both for the EEG recorded at T0 and at T1. When considering only the features calculated at T1 an AUC = 0.750 was obtained (z= 2.53, p = 0.0011, Fig. 2A-B). When employing both T0 and T1 feature, an AUC = 0.800 was obtained (z=2.75, p=0.0059, Fig. 2C-D). Lastly, an AUC = 0.610 was obtained when employing only the T0 features.

The scalp distribution of the weights of the PLS (β-weights), when the machinery was trained on T0 features and on T1 features are shown in Fig. 2A and 2C, respectively. Figure 3A reports the distributions of the β-weights for all the 152 features considered, whereas Fig. 3B depicts the β-weights associated to the top 5% of features with the largest β-weights in magnitude, i.e. those most impacting the prediction. Negative weights are thus associated to LEV non-responders (i.e. NSF

patients after two-years of LEV initiation), whereas positive weights are associated to LEV responders (i.e. SF patients after two-years of LEV initiation).

4. Discussion

In this study, we showed that the EEG modifications induced by LEV in patients with a new diagnosis of TLE can be exploited to obtain a data-driven prognostic index of long-term therapeutic efficacy (i.e. sustained seizure-freedom for at least two years). We showed the feasibility of predicting sustained seizure-freedom after LEV therapy using resting-state 19-channels EEG and optimized machine-learning algorithms (AUC = 0.8 using both T0 and T1 EEGs). It is important to note that our study was not designed as a comprehensive optimization effort to achieve maximum possible prediction accuracy. Such an effort would require additional classification models and would demand a larger population from multiple sites and additional data sets. However, to our best knowledge, this is the first attempt to apply resting-state pharmaco-EEG measures for ASMs response prediction using data-driven machine-learning algorithms (PLS regression).

The main advantages of these approaches are that the extraction of important features is left to data driven approaches. Indeed, finding the link between the multi-channel EEG, recorded before the initiation of an ASM (T0) and at 3 months after therapy (T1) and the clinical outcome of the single patient can be conceived as a multivariate regression problem (i.e. machine learning problem). The function that links the raw EEG signals, or some EEG features, and the clinical outcome can be approximated relying on supervised learning (Dietterich 2000; Chiarelli et al. 2020) with the avoidance of restricting a-priori assumptions. Moreover, data-driven approaches guarantee that, once the model is built, it can be explored to understand which features were considered relevant by the model itself and how they affect the prediction. Another important characteristic of data-driven approaches is that the model can be used for prediction on new data at a single subject level and can be updated once the outcome is known (Torrey, L., & Shavlik 2010).

Recently, we showed that EEG connectivity parameters could be used for the prediction of ASMs efficacy in TLE patients (Ricci et al. 2021). Yet, the possibility of exploiting machine-learning algorithms for the prediction of ASM efficacy using pharmaco-EEG is still an open question (Höller et al. 2018), although previous authors have hypothesized that pharmaco-EEG could "eventually predict therapeutic efficacy in patients" (Saletu et al. 1987).

In this study, we confirmed that this possibility is achievable. The effective power of different frequency bands in the EEGs performed in our cohort of patients (all drug-naïve adult patients with a new diagnosis of TLE) was able to predict clinical outcome, with the best predictive results given by the combination of T0 and T1 EEG analysis. This is crucial since the integration of quantitative EEG measurements in the initial administration of ASMs will eventually contribute to the development of future data-driven machine-learning algorithms that may aid physicians in the initial selection of ASMs for different epilepsy types. It is also important to emphasize that our analysis was performed using conventional 19-channels EEG, which is low-cost and widely available for clinical practice in most epilepsy centers. Therefore, our methodology can also be applied in most epilepsy centers without the necessity of advanced neurophysiological techniques (i.e. high-density EEG or Magnetoencephalography). Finally, it is interesting to note that the channels which impacted the most for the prediction of outcome in the machine-learning algorithms were those most strictly associated to the epileptogenic focus (temporal lobe electrodes: T3, T4, T5, T6, please see Figure 3B). This notion further supports the idea of epilepsy as a "disorder of cortical networks" (Kramer and Cash 2012; Englot et al. 2015; Assenza et al. 2020b, 2020a), and the influence that the modifications induced in these "pathological" epileptogenic networks may have for the individual prognosis of patients with epilepsy. Indeed, the modifications in effective power induce by LEV in the electrodes spatially closer to the epileptogenic focus were the most influential in predicting seizure freedom after the initiation of the ASM.

4.1 Limitations

Our study has some limitations which should be stated. The first limitation is the non-randomized, retrospective nature of the study design: although we could establish the statistical relationship between EEG effective power and clinical outcome in retrospection using supervised machine-learning, we were not able to directly evaluate the effect that such analysis had on the medical management of patients. Future studies should rely on a sample size sufficiently large to allow the characterization of specific EEG effects of different ASMs in relation to the location of the epileptic focus and to other determinant variables (i.e. age, epilepsy duration, topographical distribution of EEG changes) (Hedrich et al. 2017; Ricci et al. 2021). Moreover, although we used PLS and leave-one-out cross-validation to control the overfitting, our performance estimation is not completely unbiased. Future studies are warranted to validate the machine-learning model by validating it against an independent data set that was not used for the model construction. Finally, our model showed that the T0 EEG had the lowest predictive value for clinical outcome (AUC = 0.6). From the clinical perspective, predicting the treatment outcome from the T0 EEG data alone is preferable because this approach would accelerate treatment selection and decrease the risk of side effects of ASMs that may reveal to have an inadequate effect on seizures. Future studies employing a larger sample size will reveal whether the T0 EEG alone could be exploited in the machine-learning algorithm for the prediction of therapeutic efficacy.

4.2 Conclusions

This study provides a proof-of-concept pipeline for predicting the clinical response to ASMs in patients with epilepsy. Developed into a proper clinical application, such a pipeline may provide a valid treatment planning tool for neurologists. Future studies employing larger data sets that include several groups of patients and ASMs with different mechanisms of action may benefit from the

pipeline proposed in this study in order to develop a model that can match each patient to the most effective anti-epileptic treatment.

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Potential Conflict of Interest

None of the authors have potential conflicts of interest to be disclosed.

Ethical Publication Statement

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

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Figure Legends

Figure 1.

Methodological Design. *Step 1:* T0 (before Levetiracetam [LEV] initiation) and T1 (3 months after LEV therapy) resting state EEG recordings. *Step 2:* Effective Power calculation for four frequency bands. *Step 3:* Partial Least Square (PLS) implementation and cross validation *Step 4:* Results interpretation.

Figure 2.

A: Topographical representation of Partial Least Square (PLS) weights for T0 (before Levetiracetam [LEV] initiation) in the four frequency bands. B: Area Under the Curve (AUC) using only T1 (3 months after LEV therapy) recorded EEG as PLS input. C: Topographical representation of PLS weights for T1 in the four frequency bands. D: AUC using both T0 and T1 recorded EEG as PLS input.

Figure 3.

A: Regression weights of the Partial Least Square (PLS) performed with both T0 (before Levetiracetam [LEV] initiation) and T1 (3 months after LEV therapy) EEG data. B: PLS weights associated to the top 5% of features with the largest weights in magnitude, i.e. those most impacting the prediction (Delta δ: 2-4 Hz; Theta θ: 5-7 Hz; Alpha α: 8-12 Hz; and Beta β: 13-20 Hz).

Table 1. Patient clinical characteristics and outcome.

No.	Sex	Age, ys	Seizure Frequency	Seizure type	Aetiology	Electroclinical localization	Outcome	LEV Maintenance Dose (mg)	Adverse Events
1	F	73	Five episodes	FS with PA	Structural (Ischaemic Stroke)	Left TP	NSF (SR < 50%)	1000	No
2	M	36	Four episodes	Focal to bilateral TCS	Structural (Ischaemic Stroke)	Right FT	NSF (SR > 50%)	1000	No
3	M	64	Monthly	FS with IA	Unknown	Right T	NSF (SR < 50%)	1000	Depression
4	F	25	Five episodes	FS with IA	Structural (Cavernous Malformation)	Right T	NSF (SR > 50%)	1000	No
5	F	20	Monthly	FS with IA/ Focal to bilateral TCS	Unknown	Right T	NSF (SR > 50%)	1000	Irritability
6	M	69	Monthly	FS with IA	Unknown	Left T	NSF (SR > 50%)	2000	No
7	F	30	Five episodes	FS with IA	Unknown	Right FT	NSF (SR > 50%)	2000	No
8	F	38	Monthly	FS with IA	Unknown	Right T	NSF (SR > 50%)	1000	No
9	F	69	Monthly	FS with IA/ Focal to bilateral TCS	Structural/Infectious (History of HSV Encephalitis)	Left T	NSF (SR < 50%)	1000	Depression
10	M	64	Four episodes	FS with IA/ Focal to bilateral TCS	Structural/Infectious (Cerebral Abscess)	Left T	NSF (SR > 50%)	1000	No
11	F	24	Monthly	Focal to bilateral TCS	Structural (Hippocampal Sclerosis)	Left T	NSF (SR > 50%)	1500	No
12	M	28	Monthly	Focal to bilateral TCS	Unknown	Right T	SF	1500	No
13	F	55	One episode	FS with IA/ Focal to bilateral TCS	Unknown	Left T	SF	2000	No
14	M	26	Monthly	Focal to bilateral TCS	Unknown	Right FT	SF	1500	No
15	M	78	Five episodes	FS with IA	Unknown	Left T	SF	1000	No
16	F	58	One episode	FS with PA	Unknown	Right T	SF	1000	Drowsiness
17	M	47	Two episodes	FS with IA/ Focal to bilateral TCS	Structural (Cerebral AVM)	Left T	SF	2000	No
18	F	77	Four episodes	FS with PA	Structural (Ischaemic Stroke)	Left T	SF	1000	No
19	M	75	One episode	FS with PA	Unknown	Left T	SF	1000	Nausea
20	F	24	Four episodes	FS with IA	Structural (Cavernous Malformation)	Left T	SF	1250	No
21	F	63	One episode	FS with IA	Structural (Cavernous Malformation)	Right T	SF	1000	No
22	M	20	Monthly	Focal to bilateral TCS	Unknown	Left T	SF	1000	No
23	F	86	Monthly	FS with PA	Structural (Meningioma)	Left TP	SF	1000	No

ys = years; LEV = Levetiracetam; M: male, F: Female, FS: Focal seizures; PA: Preserved awareness; IA: Impaired awareness; TCS: Tonic-clonic seizures; T = Temporal; FT: Fronto-Temporal; TP: Temporo-Parietal; SF: Seizure-Free after two years of therapy; NSF: Non-Seizure Free; SR: Seizure Reduction; AVM = Arteriovenous malformation; HSV = Herpes Simplex Virus.

Figure 1

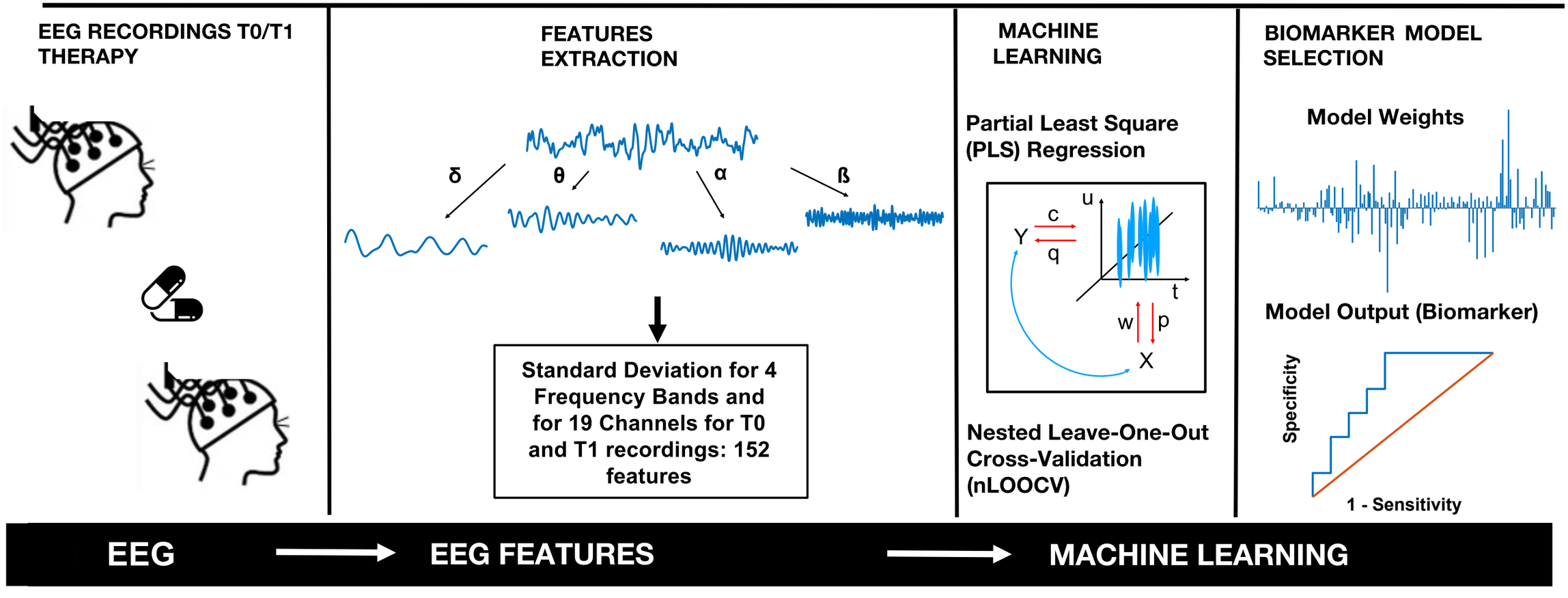

Figure 2

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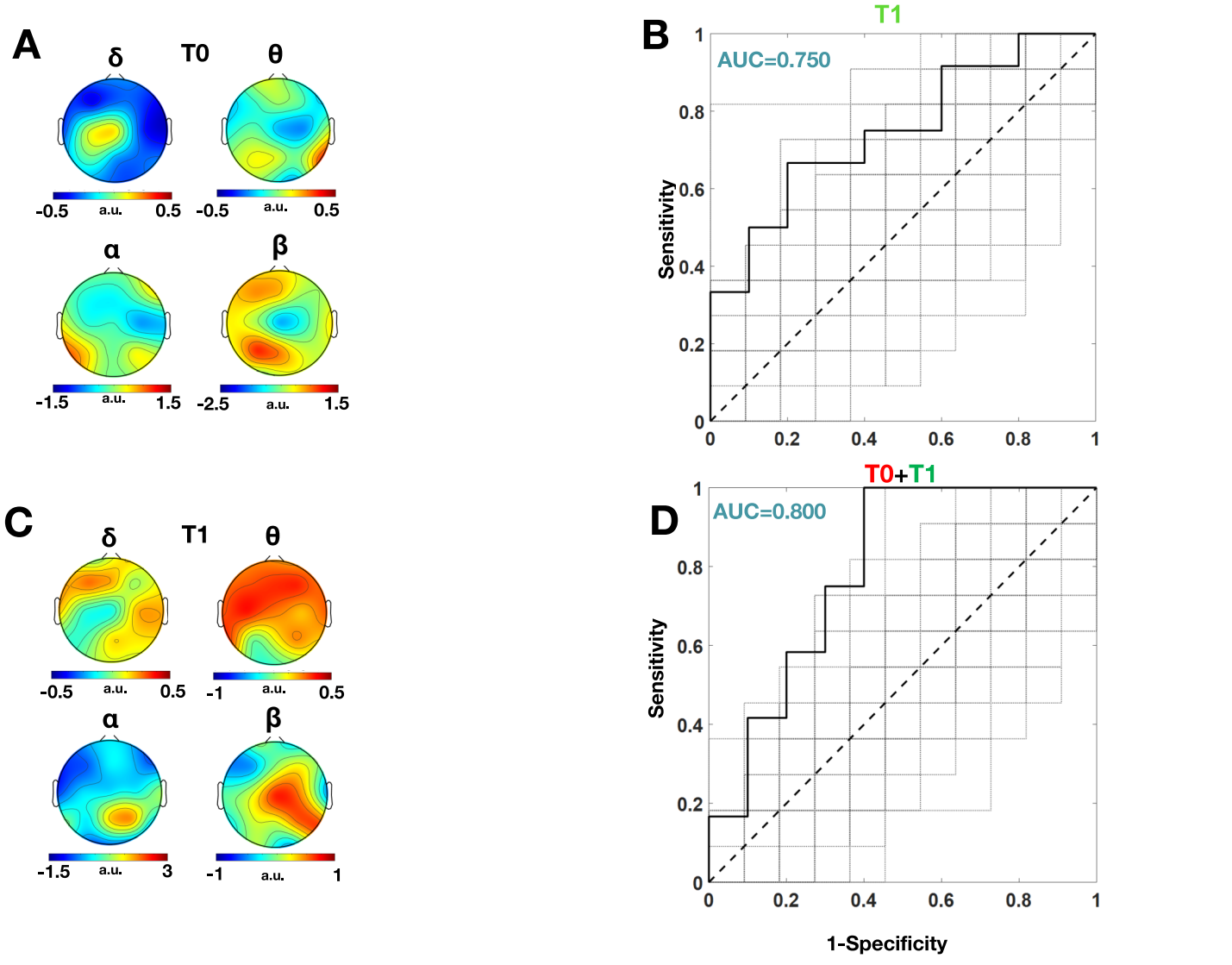

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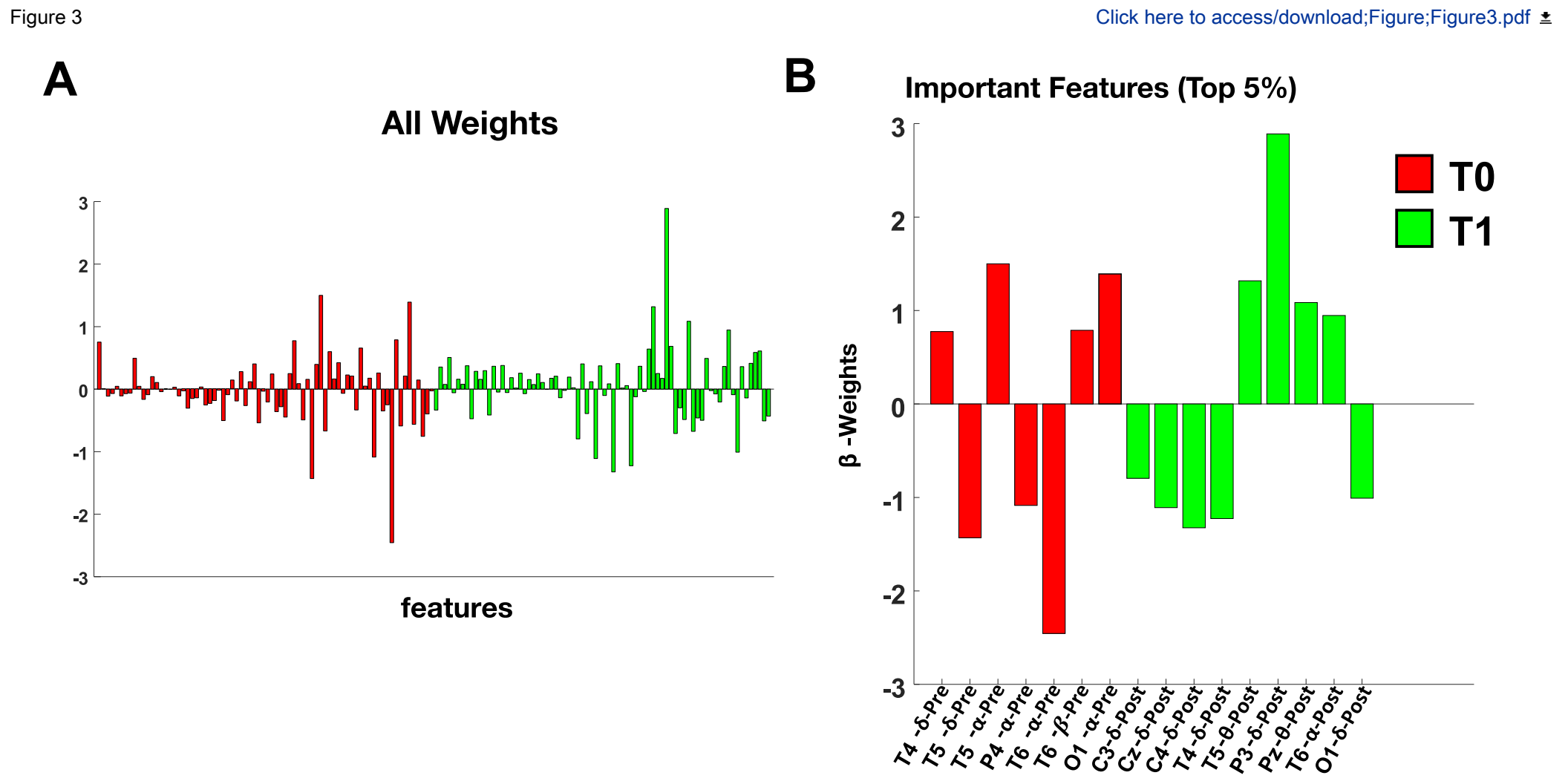

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