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Ongoing intracortical neural activity predicts upcoming interictal epileptiform discharges in human epilepsy

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Abstract

Interictal epileptiform discharges (IEDs) are a hallmark of focal epilepsies. Most previous studies have focused on whether IED events increase seizure likelihood or, on the contrary, act as a protective mechanism. Here, we study instead whether IED events themselves can be predicted based on measured ongoing neural activity. We examined local field potentials (LFPs) and multi-unit activity (MUA) recorded via intracortical 10 × 10 (4 × 4 mm) arrays implanted in two patients with pharmacologically resistant seizures. Seizures in one patient (P1) were characterized by low-voltage fast-activity (LVFA), and IEDs occurred as isolated (100 — 200 ms) spike-wave events. In the other patient (P2), seizures were characterized by complex spike-wave discharges (2 - 3 Hz) and IEDs consisted of bursts of ~ 2 — 3 spike-wave discharges each lasting ~ 300 — 500 ms. We used extreme gradient boosting (XGBoost) classifiers for IED prediction. Inputs to the classifiers consisted of LFP power spectra; In addition, counts of MUA (1-ms and 100-ms time bins) and envelope, as well as leading eigenvalues/eigenvectors of MUA correlation matrices were used as features. Features were computed from moving short-time windows (1 second) immediately preceding IED events (0.3 - 0.5 preictal gap). Classifiers allowed successful IED prediction in both patients, with better results in the case of IED occurring in the LVFA case (area under ROC curve: 0.86). In comparison, LFP features performed comparatively for P1 datasets, while MUA appeared not predictive in the case of P2. Our preliminary results suggest that features of ongoing activity, predictive of upcoming IED events, can be identified based on intracortical recordings, and warrant further investigation in larger datasets. We expect this type of prediction analyses to contribute to a better understanding of the mechanisms underlying the generation of IED events and their contribution to seizure onset.

I. Introduction

IEDs are a hallmark of epilepsies, yet little is known about how IED interact with seizure events, either by increasing their likelihood or by having a protective nature [1], [2].

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Furthermore, how IEDs themselves are generated and the conditions that increase their likelihood is poorly understood. From a dynamical systems perspective, previous studies [3] have hypothesized that IEDs may result from stochastic perturbations leading to a rapid excursion from normal states into limit cycle like transients, which then return to normal states without evolving into full seizures. This hypothesis might also be understood in the context of bifurcations, where the system transiently approaches a bifurcation point (saddle-node on invariant cycle in the previously developed models), leading to precursor changes in ongoing neural activity (e.g. loss of stability, slowing down and increase in autocorrelation functions, etc). These precursor signatures would then be predictive of IED events.

We also note that IEDs are known to show circadian and multi-day rhythms [4] and appear to be predictive of seizures over long time scales [5]. Here, we focus on extrinsic features (e.g. recent LFP and MUA features) instead of on auto-history effects of the IED point process itself. We present initial analyses attempting to detect and identify IED precursor signatures in ongoing neural activity.

We asked whether features of ongoing neural activity immediately preceding IEDs are predictive of such events. We consider both LFPs and MUA recorded intracortically via microelectrode arrays from two patients undergoing intracranial neuromonitoring as candidate for resective surgery, a possible treatment of pharmacologically resistant epileptic seizures.

LFP features included power spectra in specific frequency bands in the recorded neocortical patches. In addition, features based on MUA counts and MUA envelopes, as well as leading eigenvalues/eigenvectors of corresponding pairwise correlation matrices are used. The IED prediction problem is formulated in terms of correctly classifying or discriminating neural features computed from windows immediately preceding IEDs from those that do not.

II. Methods

A. Patients, neural recordings and signal processing

Intracortical microelectrode array (MEA) recordings were obtained from two patients undergoing neuromonitoring at Massachusetts General Hospital and Brigham and Women's Hospital under approved local IRB protocols.

MEA recordings were not part of the clinical recordings and were performed for research purpose only with the patients' consent. The MEA consisted of a 10 × 10 (4 × 4 mm) array of microelectrodes (Blackrock, Salt Lake City, UT) which were implanted in areas expected to be resected in the temporal gyrus. MEA data were recorded broadband (0.3 Hz - 7.5 kHz) and sampled at 30 kHz. More details about the MEA device and recordings can be obtained in [6], [7], [8].

Seizures in patient P1 were characterized by low-voltage fast-activity (LVFA) LFP oscillations. (More details about this patient can be found in [7].) Data from the second patient, labeled here P2, have not been presented before in our previous studies. Seizures in P2 were characterized by spike-wave complex (SWC) discharges.

Counts and envelope of MUA, as well as LFPs, were obtained from the MEA recordings as follows. For MUA count, we high-passed (> 250 Hz) the recordings for each electrode site, and counted the threshold crossings (− 3 standard deviation) in time bins of $\Delta = 0.5$ ms. For MUA envelope, we clipped the high-pass filtered signal at 3 standard deviation to emphasize the population activity and attenuate the effects of the large actions potentials emitted by neurons very close to the microelectrodes [9]. Signals were then squared and low-pass filtered (10 Hz). For the LFP, we low-pass filtered (< 500 Hz)the recorded signals. The sampling rate for these three signals was 2kHz, and filtering was performed using a Butterworth filter (order 9, zero phase design).

B. IED detection

IED events were first detected via an automated method as previously described in [10]. After this automated detection, visual inspection was used to further select IEDs that satisfied the following conditions: (a) artefact-free; (b) if events occurred in bursts (< 1 – 2 s), only the first event was kept; (c) the corresponding pre-IED time segment (see below) was also artefact-free. We hope to examine in future validation studies how different IED detection methods and procedures affect IED prediction.

C. LFP feature extraction

The LFP power spectrum was estimated in ten frequency bands (0.3-4 Hz, 4-8 Hz, 8-12 Hz, 12-18 Hz, 18-25 Hz, 25-50 Hz, 50-80 Hz, 80-150 Hz, 150-300 Hz, 300-500 Hz). We used multitaper methods [11] in consecutive 1-second time windows (no overlap) and a half-bandwidth of 2Hz. The power spectrum features of the LFP were obtained by averaging across the different frequency bands.

D. MUA feature extraction

The total number of MUA counts in each 1-second time window for each channel was directly used as a feature. We also used the leading eigenvalue and eigenvector of the pairwise correlation matrices for MUA count, MUA coarse count, and MUA envelope. To obtain the MUA coarse count, we computed the spike counts in coarser time bins of $\Delta = 100$ ms.

Correlation matrices for MUA were computed using Pearson correlation coefficients based on the 1-second count series for each channel pair. We used a range of time lags, up to ±50 ms. For each channel pair, the extremum of the lagged correlation function was selected for each time window.

With these features we could directly assess the contribution of the activation patterns across the MEA (i.e. LFP power spectrum and MUA count) or of features related to pairwise co-activation patterns (second order statistics) across the MEA (MUA correlation).

E. Definition and labeling of pre-IED and non-IED features

One-second long segments of data were selected before each IED (pre-IED samples), with a gap of 0.3 (patient 1) or 0.5 (patient 2) seconds between the end of the pre-IED segment and the detected IED. One-second long non-IED segments were randomly drawn from the signals with a minimum gap of one second between each non-IED segments and any IED events. The number of non-IED samples was three times larger than the number of pre-IED samples.

F. XGBoost classification

We formulated the problem of predicting upcoming IED events in terms of discriminating or classifying immediately preceding activity (pre-IED) and interictal samples that did not include IED events (inter-IED). There were 2188 events (547 pre-IED) in P1 and 1280 events (320 pre-IED) in P2. We used extreme gradient boosting (XGBoost), a state-of-the-art classifier [12]. XGBoost models where estimated on training data and prediction performance was assessed on test data. We randomly sampled (uniformly) 80% to generate a training set and the remaining 20% was used for the testing. The same process was repeated 10 times to obtain an average performance. The hyperparameters for the XGBoost were set to default parameters, specifically learning rate=0.3, maximum tree depth=6, minimum child length=1, and L2 regularization parameter=1. A systematic exploration of different ranges of these parameters is needed in future work.

III. Results

We examined how well XGBoost classifiers, taking ongoing LFP and MUA signals preceding IED events as input features (Methods), performed in terms of discriminating inter-IED and pre-IED events, i.e. predicting IED events. In the next sections, we describe typical IED events in these two patient datasets, assess prediction performance and examine the relative contributions of different LFP and MUA features to classification performance.

A. Examples of IED events

The morphology, time scales and temporal correlations of of IED events, as well as the seizures themselves, differed significantly across the two patients. In P1, seizures were characterized by LVFA with LFP displaying sustained narrowband gamma oscillations which slowed down gradually from ~ 60 Hz at the beginning of the seizure to ~ 30 at seizure termination. IED events tended to be sparse and isolated. They showed the characteristic spike and wave morphology but their duration was much shorter than IED events in P2, with IEDs lasting about 100 ms, as shown in Figure 1.

Seizures in P2 where characterized mostly by ~ 2-3 Hz spike-wave complex (SWC) discharges, while IEDs showed the typical spike and wave phases and tended to cluster in bursts of ~ 2-4 events as shown in Figure 2. As stated in the Methods, we selected only the first IED event in a burst to be included in the training and testing of classifiers.

B. Ongoing neural activity predicts upcoming IED events

XGBoost classifiers successfully predict IEDs in both patient datasets. Performance according to ROC analysis was better for P1 (gamma seizures, sparse/isolated IEDs) than for P2 (Fig. 3). The area under the ROC curves (AUCs) corresponded to 0.86 (P1) and 0.67 (P2). The 95% confidence intervals for chance level AUCs corresponded to [0.44, 0.57] and [0.42, 0.58] for P1 and P2 respectively. These confidence intervals were obtained on surrogate datasets generated by random permutations of the labels (200 datasets), followed by the application of the same procedures for training and testing XGBoost classifiers as done in the actual datasets. Prediction performance based on precision-recall curves (Fig. 3) was also consistent with the ROC analysis.

C. Ranking of predictive features

We assessed feature importance using two approaches. First, a feature ranking was obtained from XGBoost classifiers according to standard procedures [12]. Second, we directly compared the prediction performance of classifiers that were trained separately on only LFP- or MUA-based features. In the latter case, the comparison allowed us to contrast these two different types of signals.

XGBoost feature importance (Fig. 4) ranked LFP power spectra in the frequency band 8 - 12 Hz and 0.3 - 4 Hz as the two top features (among the 20 features ranked in Figure 4) for P1. The remaining 18 features consisted the mixed distribution of LFP power spectrum and MUA-related features (count, envelope and leading eigenvector (eigenvector centrality) of MUA correlation matrices. In contrast, the two top features for P2 consisted of power spectra in the frequency bands 300 - 500 Hz and 80 - 150 Hz and a mixed distribution of LFP- and MUA-based features where the domination of LFP power spectrum features was observed.

Direct comparison of LFP- vs MUA-based features revealed that both feature sets performed comparatively for P1 (Fig. 5). In contrast, XGBoost classifier using MUA-based features only showed prediction performance close to chance level, suggesting that the examined features of ongoing MUA activity in P2 did not carry information about upcoming IED events (Fig. 5), which agrees with our calculated XGBoost feature importance (Fig. 4) for P2.

IV. Discussion

Interictal discharges (IEDs) appear as sparse transient epileptiform discharges (either as isolated events or in bursts) and are a dominant feature in neural activity in various types of epilepsy. Little is known about the mechanisms underlying their generation, how they relate to ongoing activity, and whether they might promote or reduce the likelihood of upcoming seizures. Here, we focused on the study of whether ongoing cortical activity modulates the likelihood of IED events in people with pharmacologically resistant seizures undergoing neuromonitoring prior to resective neurosurgery for seizure treatment.

Our findings revealed that ongoing intracortical signals such as LFPs and MUA recorded via MEAs are predictive of upcoming IEDs. In particular, power spectrum in different frequency bands and MUA features allowed high prediction performance (area under ROC curve = 0.86) in a patient with LVFA seizures. Prediction performance in the other patient (SWC seizures, and slower IEDs) was lower (area under ROC curve = 0.67) but still significant.

Our feature importance analysis showed that LFP and MUA contributed about equally to IED prediction in P1, while MUA was not informative, for the our choice of features, in P2.

It remains an open question how predictive information in the selected features relate to actual neural dynamics in the neocortical patches. As stated earlier, IEDs are hypothesized to result from stochastic perturbations leading to rapid transients excursions away from normal ongoing states and then back (e.g. [3]. We hope to examine in future studies whether changes in the measure LFP power spectra, MUA and related spatial correlation measures relate to transient stability changes and increased stochastic fluctuations in ongoing cortical activity in the recorded neocortical patches.

We also note that we focused here only relatively fast changes in ongoing neocortical activity. IED activity is known to show also circadian and multi-day rhythms (e.g. [4]). Examination of ongoing neural dynamics at these much slower time scales remain a problem for future studies.

Our intracortical MEA recordings were obtained from patients in the Epilepsy Monitoring Unit during the neuromonitoring period. During this period, anti-epileptic medication is gradually reduced so that seizures can be more easily recorded to guide identification of seizure onset areas for resective neurosurgery. This reduction in medication also increases the rate of IED occurrence. After seizure onset areas are identified, medication is resumed at the original level, reducing also the IED rates. This is an example of confounding factor, not only on IED rates but also potentially on their underlying mechanisms, that should be better controlled in future studies.

We hope to explore the potential translational role of the IED prediction approach presented here in future studies. One possibility is that IED prediction could guide neuromodulation for seizure control. For example, in the scenario that IED events tend to increase seizure onset likelihood [1], neuromodulation can be delivered at periods of predicted IED occurrence in order to decrease their rate. On the other hand, if IED events have a more protective nature againt seizures [2], a different neuromodulation intervention can be delivered at periods of predicted IED occurrence in order to increase their rate.

V. Summary and Outlook

Our findings provide preliminary evidence supporting that ongoing cortical activity modulates the likelihood of interictal epileptiform discharges in people with pharmacologically resistant seizures. This modulation was detected in two patients who showed two distinct types of seizures (LVFA vs SWC seizures) and IEDs with two different morphologies and time scales. Given the small sample in our study, these preliminary findings warrant further studies in larger datasets.

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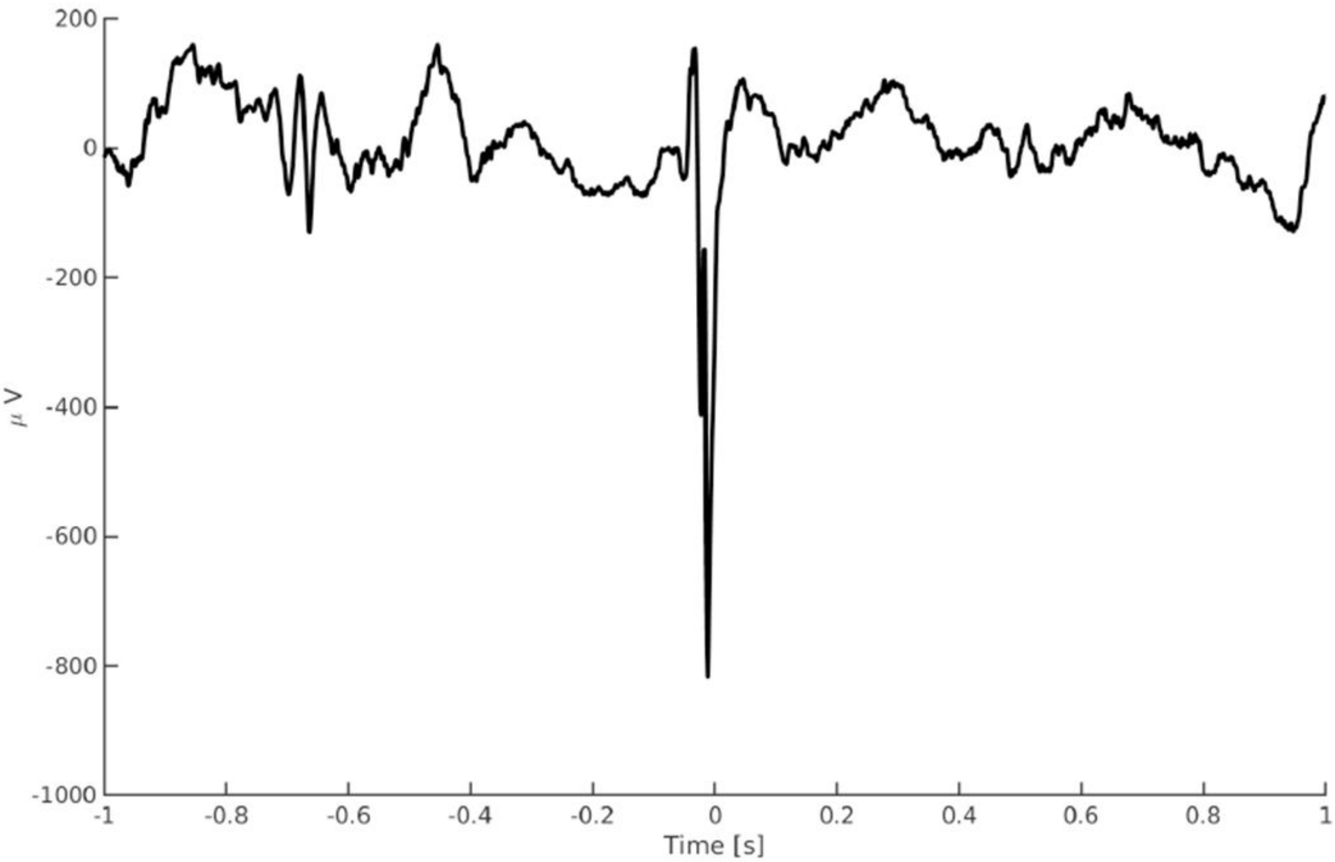

Fig. 1.

Example of IED in patient P1 (LVFA / gamma seizures). The interictal discharge (centered at time zero) in this example shows the characteristic spike (fast negative deflection) followed by by slower wave (positive deflection). The entire event lasts about 200 ms.

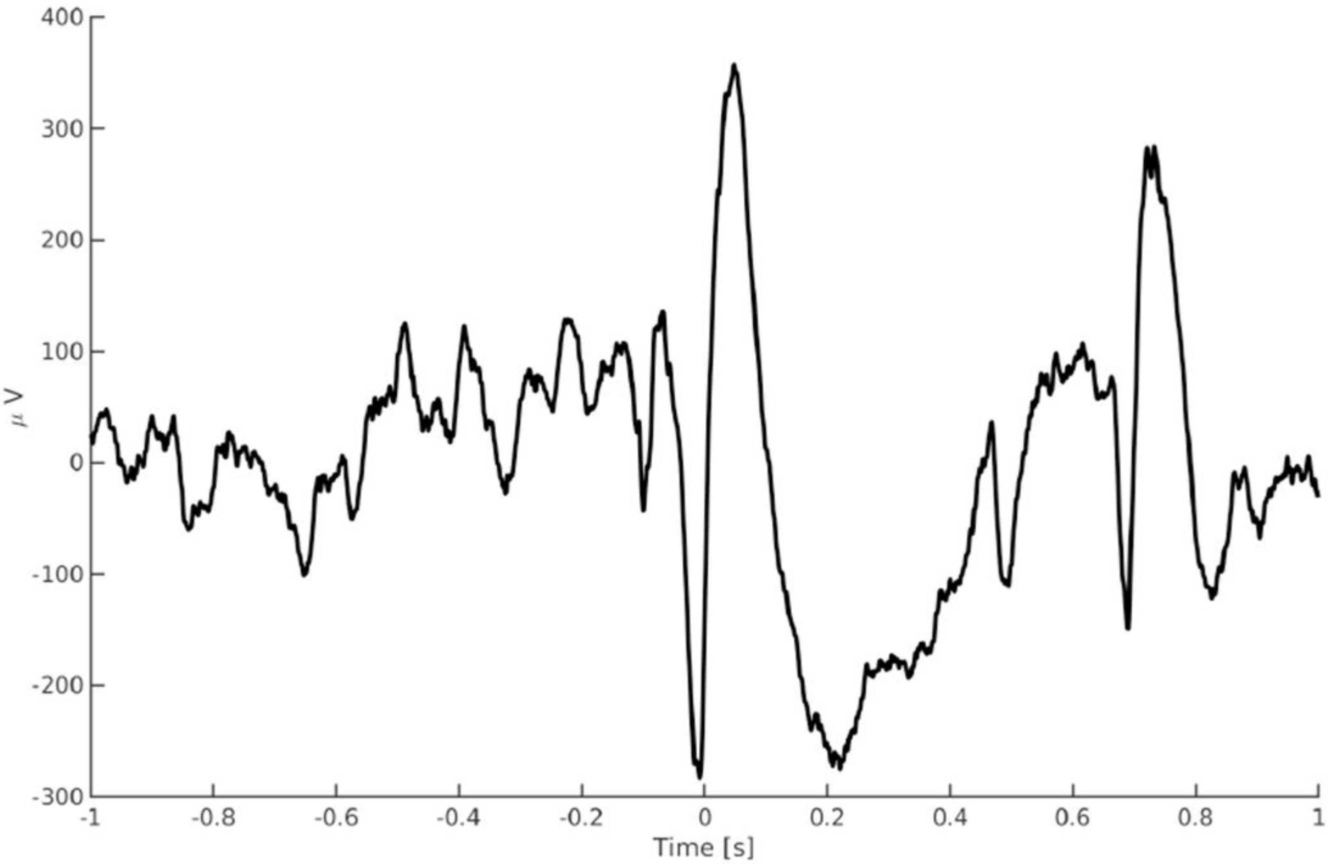

Fig. 2.
Example of IEDs in patient P2 (SWD seizures). In contrast to P1, IEDs for this patient were slower, showed more complex morphology and could occur in bursts. (In this example one case see at least two consecutive events, with the first event centered at time zero.) When bursts ocurred, only the first IED was included in the prediction analysis.

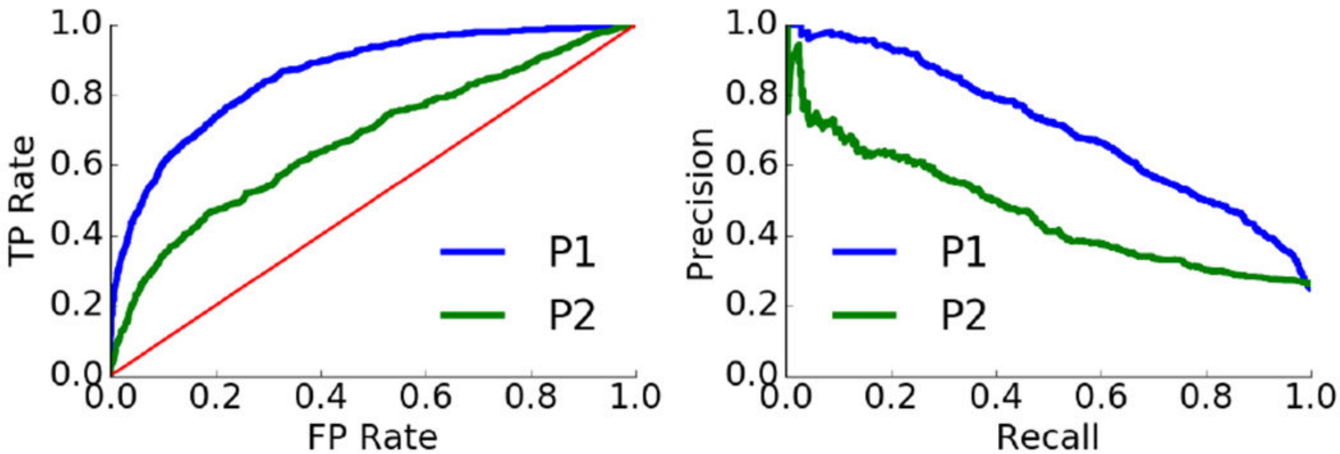

Fig. 3.

Classification performance. Left: ROC curves for patients P1 and P2. Right: Precision-recall curves for P1 and P2. XGBoost classifiers used both LFP- and MUA-based features. Classification performance was assessed on test datasets. The area under the ROC curves corresponded to 0.86 (P1) and 0.67 (P2).

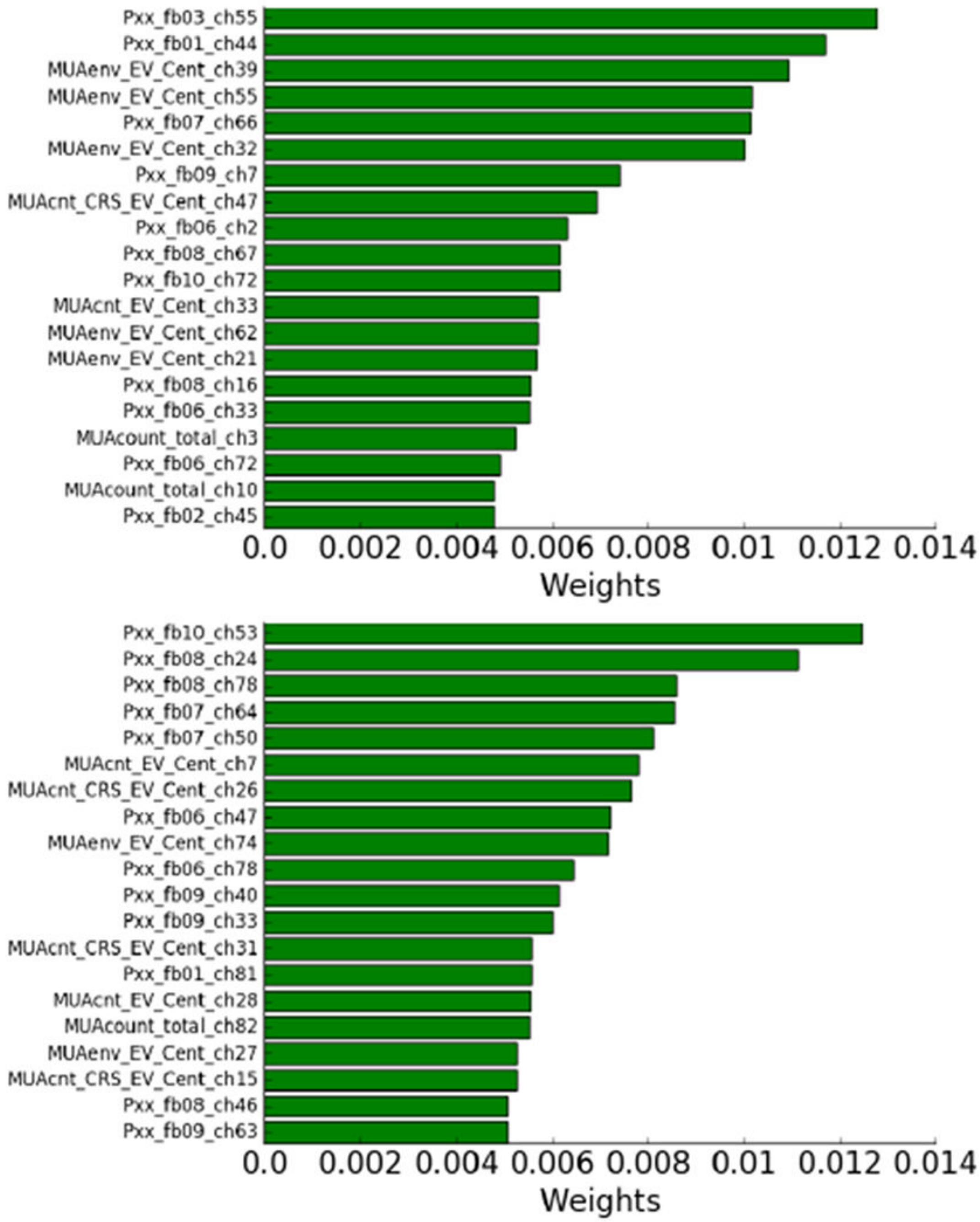

Fig. 4.

Feature ranking based on XGBoost classifiers for P1 (top) and P2 (bottom). Feature importance (“weights”) are ranked from top to bottom in each plot. “Pxx_” denotes power spectrum is a given frequency band; “MUAcount_” denotes MUA count; “EV_Cent_” denotes eigenvector centrality (leading eigenvector of the MUA correlation matrix).

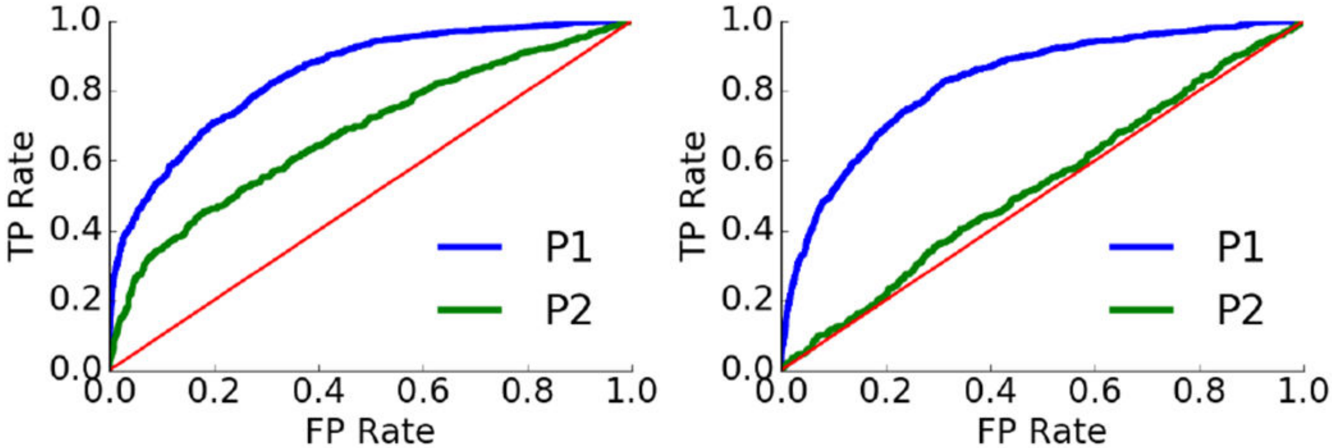

Fig. 5.

Feature ranking: LFP vs MUA. The left plot shows the ROC curves for XGBoost classifiers trained only on the LFP-based features. The right side shows the same for the case of MUA-based features only. The area under the ROC curves corresponded to: 0.85 (LFP) and 0.83 (MUA) for P1, and 0.68 (LFP) and 0.53 (MUA) for P2.