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The introduction of deep brain stimulation (DBS) has probably been one of the most illustrious advances of the last 30 years for the management of neurologic disorders like Parkinson's disease (PD), essential tremor, and dystonia. The delivery of low electric currents via stereotactically implanted electrodes to a specific brain target preferentially modulates distinct neural networks, providing clear clinical benefit (Muthuraman et al., 2018a). In PD, e.g., conventional DBS continuously stimulates the subthalamic nucleus (STN), a region within the cortico-basal ganglia network, with frequencies between 130 and 180 Hz, efficiently reducing cardinal symptoms like bradykinesia or resting tremor in eligible patients.

Despite its clinical efficiency, the exact mechanisms by which DBS modulates local and long-range neural activity to improve motor symptoms remain elusive. Accumulating evidence demonstrates that DBS decreases pathologically enhanced beta-band power (i.e. oscillatory activity with frequencies between 13 Hz and 30 Hz) within the basal ganglia–cortical loops. These modulations correlate with ameliorated bradykinesia and rigor, suggesting a possible causal relationship between oscillations and these symptoms (Brittain and Brown, 2014; Tinkhauser et al., 2018). However, the pathophysiology of tremor generation clearly differs from that of bradykinesia and rigidity, given that the magnitude of tremor is not correlated to dopamine deficiency in the striatum or the beta-band power in the STN or pallidum (Hallett, 2012; Beudel and Brown, 2016).

In addition to the challenges arising from different pathological mechanisms, PD symptoms often fluctuate dynamically, depending on factors such as cognitive and motor load and concurrent pharmacological treatment (Little et al., 2013). The continuous delivery of pulses in conventional DBS rigidly modulates the networks even at times when it might not be necessary, potentially increasing the risk of side effects or exhibiting less efficient long-term results. The unnecessary high power consumption means that the battery has to be recharged more often and replacement surgeries have to be carried out sooner. Tailoring DBS to specifically target distinct symptoms individually and dynamically could substantially improve its clinical efficiency while preserving battery life and limiting side effects. For example, it could prove useful to have different DBS parameters for different symptoms, which are only turned on when these symptoms appear.

A novel approach to address such issues consists of uncovering patient-inherent bio-signals to control the stimulation in a closed-loop fashion, called adaptive DBS (aDBS) (Muthuraman et al., 2018a). Continuously recording and analyzing biophysical signals that have been previously linked to disease related symptoms should be provided in a robust framework that may guide decisions about when to turn DBS on or off, or adapt the stimulation parameters. Local field potentials (LFP), which can be readily and easily recorded by DBS-electrodes, provide the possibility to analyze continuous electrophysiological responses that may carry sufficient information to detect and discriminate PD-symptoms. Thorough work has been done to investigate gamma oscillations or STN-beta-band power as potential markers for aDBS to specifically target hyperkinesia or bradykinesia, respectively (Swann et al., 2016; Tinkhauser et al., 2017). However, so far no parameter has been found that can solely identify tremor or robustly detect different tremor types.

In this issue of *Clinical Neurophysiology*, Yao et al. (2020) address the feasibility of using machine learning algorithms to detect clinical episodes of resting tremor in PD patients on the basis of tremor-specific LFP-features. Tremor is clinically defined as an involuntary rhythmic, oscillatory movement of a body part that functionally impairs the coordination and execution of targeted movement. Although different types of tremor may occur in PD, resting tremor is the most prevalent form, referring to a 4- to 6-Hz oscillating movement of a relaxed limb, which is suppressed during movement initiation. Both the basal ganglia and the cerebellum are involved in Parkinsonian tremor (Hallett, 2012). Current models suggest that the dopaminergic dysfunction in the basal ganglia triggers the onset of tremor, while the cerebello-thalamo-cortical circuits are responsible for regulating the tremor amplitude (Chen et al., 2017). It has been shown, e.g., that the amount of information outflow from the cerebellum to cortical regions correlates with tremor severity (Muthuraman et al., 2018b).

Machine learning algorithms use multidimensional information of the data of interest to train a classification- or regression model (Camacho et al., 2018). The main advantage is that features with individually low discriminative power can achieve better classification performance when analyzed synergistically. Previous research presented the general feasibility of machine learning algorithms using LFP-derived features to classify tremorous and non-tremorous episodes (Bakstein et al., 2012; Hirschmann et al., 2017; Shah et al., 2018). An artificial neural network algorithm trained with features of the LFP was able to detect tremor and

non-tremor episodes relatively accurately in 4 out of 8 patients (Bakstein et al., 2012). Recently, Hirschmann et al. (2017) showed that a Hidden Markov model based on four frequency domain features provides good accuracy, sensitivity, and specificity in PD resting tremor state-estimation. Aside from that, a logistic regression has also been able to detect Parkinsonian rest tremor combining both frequency and time domain features (Shah et al., 2018).

Following these studies, Yao et al. (2020) compared the performance of several machine learning algorithms based on a variety of features derived from LFP recordings of 12 PD-patients. Additionally, the application of a Kalman filter to the feature time-series to reduce nonlinear noise inherent to neural systems improved the specificity. Furthermore, limiting the number of features based on evaluating their discriminative power further improved the best performing classifiers' detection rate.

Importantly, the time required to analyze and detect symptoms is a crucial aspect for successful implementation of machine learning algorithms into closed-loop DBS, where the stimulation should ideally anticipate the occurrence of specific symptoms. In this context, Yao et al. (2020) are the first to report the detection latency of their classifiers. However, it should be noted that the LFP-signals recorded were subjected to offline-analyses. Given the relatively high processing demands of the applied machine learning algorithms, further research needs to be done to evaluate and optimize the latencies for analytical steps online. Moreover, additional emphasis should lie on selecting electrophysiological or analytical features that could be robustly translated into the clinics.

Declaration of Competing Interest

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

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