EDITORIAL

The Democratic Aspect of Machine Learning: Limitations and Opportunities for Parkinson's disease

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Currently, great efforts are being put toward the early identification of preclinical, biological, clinical, and laboratory markers that are able to predict the conversion of "cognitively intact" patients to overt dementia.

An example of a successful biomarker for neurodegenerative disorders, and specifically of conversion from early stage of dementia of Alzheimer's disease or Lewy body dementia (encompassing dementia with Lewy bodies and Parkinson's disease (PD) dementia)[1-3] and of progression of the diseases from mild to more pronounced stages of dementia,[4] is represented by resting state, eyes-closed electroencephalographic (EEG) rhythms. Patients with dementia exhibit a general reduction of power in the alpha and beta bands and high power of widespread delta and theta rhythms when compared with nondemented patients.[5] Specifically, dementia is associated with dominant frequency variability with the appearance of a prealpha (a fast theta rhythm of 5.5-7.5 Hz) band, now listed as a supportive biomarker in the latest consensus criteria for the diagnosis of dementia with Lewy bodies,[6] and a progressively increased relative power of theta band is described in PD dementia patients as cognition declines.[7]

The renaissance of applying clinical EEG to dementia in neurodegenerative diseases has been associated with the development of new analytical methods and breakthrough discoveries pertaining to the neuronal mechanisms underlying EEG features. Quantitative EEG (QEEG) is a derivative of regular EEG in which an offline analysis of frequency and amplitude allows the identification of specific, discrete patterns of brain wave activity. It is important to note that the source analogical data must first be visually inspected and evaluated by an expert neurophysiologist before mathematical translation of the data occurs. A thorough understanding and firm knowledge of clinical EEG features, and of mathematics and computing science, is required to prevent erroneous interpretations of digitally displayed mathematical constructs (eg, amplitude, frequency, coherence maps).

The application of artificial intelligence, and more specifically machine-learning techniques, to EEG signal analysis is one possible solution that will allow wider application of EEG analysis in clinical practice as it does not require a deep knowledge of the internal workings of the machine when processing input data to give output results, assuming that machine learning could be envisioned, in clinical practice, as a "black box" (although it is not, strictly).

The black box metaphor, which dates back to the early days of cybernetics and behaviorism, typically refers to a system in which we can observe only the inputs and outputs, but not the internal workings. To entirely understand the internal workings would require a meta system, that is, a system with a higher degree than the system itself that allows one to examine the internal working of the system from the outside. This essentially represents a variation of the Gödel incompleteness theorems, whose explanation is well beyond the scope of this editorial.

Machine-learning algorithms use mathematical, computational methods to derive information directly from data without applying predetermined mathematical models or equations. These algorithms adaptively improve their own performances as the analyzed examples increase in number. Machine learning might thus appear as the keystone of replacing human intelligence when interpreting complex signals (including EEG signals) and applying the results to routine clinical practice. It is important to distinguish between learning tasks that human examiners can already do well and learning those tasks where physicians have only limited success.[8] Interesting examples of machine learning in medical research are algorithms that allow computers to make increasingly accurate predictions to prevent infectious epidemics,[9] improve global health,[10] or accurately and timely diagnose tumors[11] or rare diseases.[12] These are examples of a supervised learning method where the computer is provided both the input dataset and

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information related to corresponding results, such that the system can reuse the same rule to link input and output data in future applications. Supervised learning focuses on classification and prediction. Notably, these are tasks that a trained person can already perform well, so the machine is often trying to approximate human performance. However, although it may be true that in most cases machine learning can at its best barely approximate the performance of a highly trained human, this assumption does not necessarily apply to untrained human brains (eg, physicians who are not trained in neurophysiology or mathematics but who are interested in classifying cognitive decline in a PD dementia patient based on EEG theta power).

In this issue, Betrouni and colleagues[13] applied pattern recognition of theta band power in EEG to categorize the degree of cognitive impairment in patients with PD.

Machine-learning approaches differ from the traditional statistical tools that researchers are trained to apply and interpret based on established reporting standards (eg, *P* value for statistical significance). As the field becomes more data intense and the use of machine learning continues to increase, good practices for conducting and reporting research at the intersection of neurophysiology and machine learning are needed to ensure that conclusions are valid and reproducible.[8]

Advanced analytical techniques to extract informative features from these data and model underlying relationships that cannot be modeled with traditional statistical tools have the potential to transform biomedical research, as they have done with autonomous driving or speech recognition. There is a distinction between algorithms that consists of instructions followed by the computer to complete a particular task and models that are derived from the application of algorithms to data.[9]

One approach to build classification models using a transformed set of features in much higher dimensions is support vector machine. Prototype methods, such as k-nearest neighbors, instead reject the idea of building a model and make predictions based on the outcome of similar case examples.[8,13] The best guess for whether a PD patient has a specific type of cognitive impairment is to see if similar patients (with the same EEG theta power) tend to have the same type of impairment.[13] All of these choices have free parameters to fit and require a learning step to optimize their parameters. In the study by Betrouni and colleagues,[13] this was the allocation of PD patients to a specific group of degree of cognitive impairment based on EEG theta power.

When the number of features is larger than the number of observations, there is a high risk of overfitting a model, which may then perform poorly on new data. The inability to learn an adequate model as a result of insufficient observations and a large feature space is often referred to as the *curse of dimensionality*.[14]

Efforts to make data analyses accurate are exemplified by the use of feature extraction algorithms, such as principal component analysis, which reduces dimensionality to make analyses more tractable.[14] Good feature engineering is a key step in building models from high-dimensional data, as it can lead to high model performance even with simple algorithms, such as naïve Bayes or logistic regression.

As Betrouni and colleagues[13] point out, data characterizing human phenomena are often high dimensional and heterogeneous and growing in volume as new tools are developed. Thus, they often do not satisfy assumptions required for parametric testing. Betrouni and colleagues[13] applied support vector machine and k-nearest neighbors classifiers on readily available data, namely QEEG data in different frequency bands and demographic characteristics, to discover the best combination of features able to predict the level (groups 1 to 5, from normal to severe) of cognitive impairment in a cross-sectional study of PD patients.[14]

The authors described a decrease of rapid (alpha and beta) and increase of slow (delta and theta) rhythms as related to increasing levels of cognitive impairment. This was already well known in literature,[7] but the added value of the work presented is the suggestion that combining QEEG and clinical features provides a classification at the individual patient level. However, a major problem of the work is the small sample size, especially in 2 groups (4 and 5) characterized by the highest level of cognitive impairment.

This not only makes it difficult to draw strong conclusions from the applied model but also exposes the model to the risk of curse of dimensionality, which the authors tried to overcome by reducing the number of EEG features used as predictor; they kept mainly slow (delta and theta) and rapid (alpa or beta) cortical rhythms as predictor variables.

Classically, patients' cognitive status is classified using cognitive testing. In the study by Betrouni and colleagues,[13] starting from an initial characterization using neuropsychological examinations, QEEG features associated with each subtype were used to train supervised algorithms. Thereafter, the models were set up to define the cognitive profile of each individual patient. The authors claim that QEEG features could serve as gatekeepers for further cognitive examinations, that is, they would serve as preliminary screenings to predict a patient's cognitive profile and to assist in the decision whether to direct a patient to second-level, more detailed cognitive testing.

It is questionable, though, if using QEEG would be more efficient and cost-effective than simply screening patients with preliminary cognitive tests. Furthermore, QEEG cannot predict which kind of second-level cognitive testing should be applied later because it cannot predict and classify from which kind of cognitive

impairment a patient is suffering (note that the model described by Betrouni and colleagues[13] was unable to differentiate group 4 with dysexecutive features and group 5, which was characterized by more evident memory deficit). Moreover, the argument in favor of the gatekeeping role of QEEG is at risk of circularity. It is unlikely that a QEEG model could add more information than the preliminary cognitive testing, if the latter were the primary method to obtain data to feed the machine.

These critical comments should not be interpreted as suggesting that QEEG is not valid as a screening tool, but it should be regarded at this point as a complement to cognitive screening. The machine-learning approach adds value to help even untrained physicians assess and manage cognitive impairment in PD patients.

A further development of machine-learning models could be aimed at selecting and combining the most discriminative QEEG features for each subtype of cognitive impairment (dysexecutive vs. amnestic, vs. visuospatial, etc.), and it is possible that topographic scalp representations of specific EEG rhythms may identify and help categorize abnormalities of specific brain regions involved in different neurodegenerative conditions.

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