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Summary

EEG is an important tool in diagnostic and prognostic evaluation of patients in the Intensive Care Unit. Current gold standard in EEG interpretation remains frame-by-frame visual analysis by a qualified encephalographer. This procedure requires highly trained clinicians, is very time-consuming, and often lacks good inter-rater agreement. Computer-based approaches (quantitative EEG; qEEG) allow for faster analysis of long recordings, and for more objective findings. In addition to emulate classical visual analysis, qEEG can provide additional information, which would not be easily apparent to a human observer.

This review presents different qEEG methods that have been proposed in ICU, with a particular focus on the crucial issue of outcome prediction after cardiac arrest. We conclude by discussing possible future development of qEEG in the light of the recent successes of so-called deep-learning.

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Key words: Quantitative EEG analysis, ICU, coma, prognostication

Quantitative EEG-Analyse auf der Intensivstation

Das Elektroenzephalogramm (EEG) spielt bei Patienten auf der Intensivstation sowohl zur Diagnostik als auch zur Prognoseabschätzung eine wichtige Rolle. Der Goldstandard zur Interpretation des EEGs ist zurzeit die visuelle Analyse durch einen erfahrenen Epileptologen. Diese Art der Analyse ist aber einerseits sehr zeitintensiv und setzt hochqualifizierte Kliniker voraus, andererseits bestehen dabei häufig auch deutliche inter-individuelle Unterschiede bzgl. der Interpretation des EEGs. Im Gegensatz dazu erlauben computerbasierte Ansätze (quantitative EEG-Analyse; qEEG) eine schnellere Analyse der EEG-Aufzeichnungen und lassen eine objektivere Analyse zu. Zudem kann die quantitative EEG-Analyse Aspekte hervorbringen, welche dem Menschen bei der visuellen Analyse verborgen bleiben. Die vorliegende Übersichtsarbeit beschreibt die verschiedenen Methoden der quantitativen EEG-Analyse bei Patienten auf der Intensivstation und fokussiert sich insbesondere auch auf das wichtige Thema der Prognoseabschätzung bei komatösen Patienten nach Herzstillstand. Abschliessend wird zudem auf die Entwicklungen der qEEG-Analyse im Hinblick auf die kürzlichen Erfolge von „Deep learning" eingegangen.

Schlüsselwörter: Quantitative EEG-Analyse, Intensivstation, Koma, Prognoseabschätzung

L'électroencéphalographie quantitative aux soins intensifs

L'électroencéphalographie reste un outil diagnostique et pronostique indispensable dans la prise en charge des patients aux soins intensifs. Le gold standard de l'interprétation de l'EEG reste l'analyse visuelle page par page par un(e) médecin spécialisé(e) en épileptologie. Ce procédé peut prendre beaucoup de temps et il reste par nature subjectif. L'analyse assistée d'un ordinateur (électroencéphalographie quantitative; EEGQ) permet une interprétation plus rapide et plus objective. En plus de faciliter l'analyse visuelle conventionnelle, l'analyse quantitative permet d'extraire des informations du tracé d'EEG que l'œil humain ne distingue pas forcément.

Cette revue présente différentes techniques d'EEGQ utilisées aux soins intensifs, en particulier pour la question essentielle de la prédiction de l'évolution clinique après arrêt cardiaque. Nous concluons par une discussion sur les possibles futurs développements de l'EEGQ dans le contexte des succès récents de l'apprentissage profond («deep learning»).

Mots clés : Electroencéphalographie quantitative, soins intensifs, coma, prédiction

Introduction

Because it directly reflects the activity of neurons, EEG plays an important role in the diagnostic and prognostic in critically ill patients, in whom the neurological examination is inevitably limited. Indications for EEG in the ICU are multiple: to rule out a non-convulsive status epilepticus in all patients with unexplained alteration in mental status, and to monitor the effect of seizure-suppressant treatment; to assist with prognostication, in particular in patients with post-hypoxic encephalopathy after cardiac arrest (CA); or to detect delayed ischemia in comatose patients with intracerebral hemorrhage in whom neurological examination is unreliable [1]. In addition, EEG can help to identify the cause of coma. Triphasic waves with sagittal (i.e. anterior-posterior or posterior-anterior) phase lag are suggestive of metabolic-toxic encephalopathy, and periodic lateralized discharges might point to limbic encephalitis. These indications have been presented previously in "Epileptologie" (see issues 4/2012 and 2/2014).

In spite of its usefulness, EEG also has several limitations. Despite the attempt to propose standardized interpretations [2], inter-rater agreement remains poor. For instance concerning prognostication after CA, the classification of EEG patterns in prognostic categories varies between studies [3 - 5]. Prognostication is further complicated by the fact that similar patterns can reflect different conditions depending on the timing of the EEG [6]. Moreover, accurate interpretation of EEG requires intensive training and long experience, and can be time-consuming. Most peripheral hospitals will not have an electroencephalographer at disposal during nights or weekends. Even in large centers, long-time recordings cannot always be interpreted in real time, which delays therapeutic interventions.

Quantitative EEG (qEEG) is a tentative approach to circumvent many of these limitations. In short, qEEG is a computer/algorithm-based analysis of EEG. Some authors distinguish the cases where some patterns are automatically recognized in the raw EEG data ("automatic detection") from cases where the EEG signal is transformed prior to automatic analysis. We will refer to both procedures as qEEG.

The aim of this contribution is to give a general overview of the possibilities and limitations of qEEG to an audience not familiar with quantitative methods. We have organized the presentation based on the goals of the different studies, namely to better characterize classical EEG patterns in order to differentiate subtypes; to serve as surrogate electroencephalographers; or, by contrast, to provide the clinicians with additional information that cannot be obtained by a human interpreter. While necessarily arbitrary, this classification has the merit to enforce a fundamental rule of all quantitative approaches: The necessity to first precisely define a question, before hoping to get a meaningful answer from an algorithm.

Quantitative characterization of classical EEG patterns

Generalized periodic discharges (GPD) are a classical EEG pattern recorded in ICU patients, especially after CA, in which case it is usually associated with an unfavorable outcome. In order to increase the diagnostic yield, several studies have tried to identify sub-types of GPD, based on the persistence of a continuous background, on the morphology and the frequency of periodic discharges. In a recent study by Ruijter et al. [7], two qEEG measures were used to assess these aspects more quantitatively in a cohort of patients with post-anoxic encephalopathy. The first qEEG measure was used to quantify the background continuity. It was defined as follows: Continuity = T_{norm}/ (T_{norm} + T_{supp}), where T_{norm} denotes the time during which the EEG amplitude exceeds 10 uV, and T_{supp} the time during which the amplitude is below this threshold. This example represents an ideal qEEG measure: The definition is unambiguous, easily implemented in an algorithm, and extremely fast to compute, so that it can be used even on-line for several days of recordings. In addition, the meaning of this formula is intuitive, because it is easily visualized. There is only one parameter, namely the threshold for defining "suppression". The authors could show that patients with good outcome had a significantly higher continuity index than patients with poor outcome.

Next, the authors wanted to characterize the frequency, periodicity, power, and similarity of discharges. These measures are again straightforward to implement, once the individual discharges have been identified. This implies that the discharges must be marked manually, or automatically with a detection algorithm prior to analysis. To this end a modified version of an algorithm originally developed for the detection of epileptic spike trains in neonatal seizure was invoked, with customized threshold values. In contrast to the continuity measure discussed above, the epileptic spike train detector however is much less intuitive, and relies on several parameters that the user has to set by hand, the effects of which are not immediately obvious. The agreement of the epileptic spike detector with visual inspection by an experienced encephalographer was less than 80%. This example illustrates the dilemma sometimes encountered with qEEG used for pattern recognition: algorithms are more error-prone, but much faster than visual analysis – a crucial point in order to analyze large amount of data. The authors could show that occurrence of status epilepticus prior to improvement to a continuous pattern was highly specific for unfavorable outcome. Other features associated with unfavorable outcome were lower discharge frequency, higher discharge power and periodicity.

In another study, the same group investigated a sub-type of burst suppression patterns, namely "burst-suppression with identical bursts" [8]. In a collective of 970 EEGs, burst-suppression with identical bursts occurred only after CA (and not, for instance, during anesthesia). QEEG was used to define an objective measure: two bursts are identical if their maximum-lagged cross-correlation exceeds 0.75. Interestingly, one EEG initially selected by visual-analysis as having identical bursts was not detected by the algorithm. The reason was the short duration of the bursts compared to the time window used for cross-correlation, which illustrates the critical role of parameters in most qEEG methods.

Reactivity, namely the modification of the EEG pattern following tactile or auditory stimulus, is a classical characteristic of EEG analysis in comatose patients. Preserved reactivity is for instance associated with favorable outcome after CA [9]. In most cases, reactivity is judged solely by visual inspection. A few studies have tried to propose more objective definitions of reactivity based on quantitative measures. Noirhomme et al. [10] compared the power spectrum for one-second time-windows before and after stimulations. The EEG was considered as being reactive if at least 50% of the stimulations induced a significant modification in the peaks of the power spectrum in at least a given number of electrodes. In most cases the interpretation by the qEEG algorithm was in accordance with that of human encephalographers. In one case, present reactivity judged by visual inspection was not detected by the algorithm (and the patient survived). On the other hand in six cases the algorithms detected reactivity against the opinion of the experts: in two of these cases the algorithm was misled by burst suppression, in one case

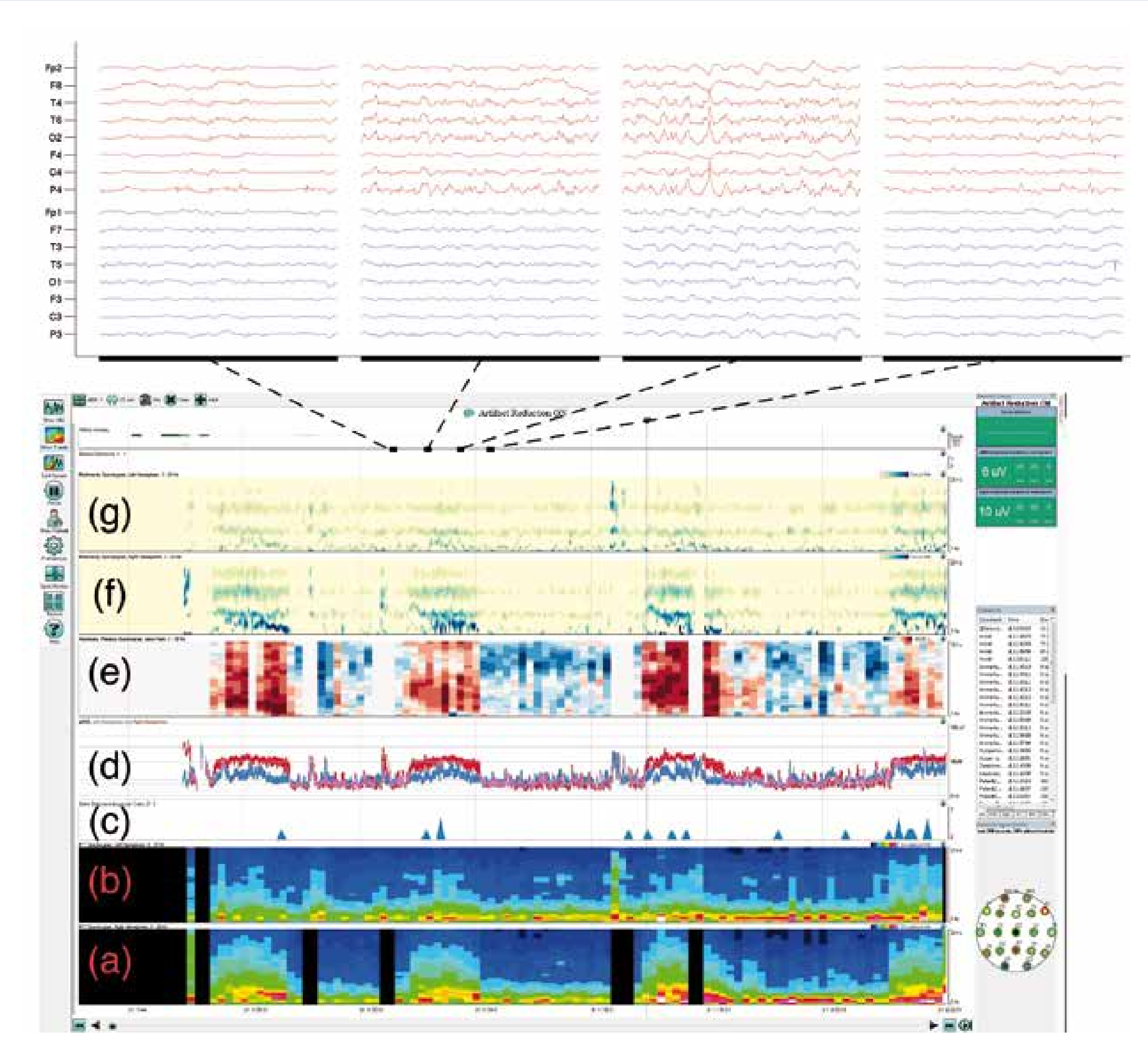

Figure 1: (Top) Focal epileptic seizure in the right hemisphere recorded in the ICU (four 5-second epochs). (Bottom) Analysis by a commercial software («Persyst») of a 30 minutes recording with 4 seizures, from the same patient. (a) Spectrogram of the right hemisphere; (b) Spectrogram of the left hemisphere; (c) Spike detection; (d) Amplitude integrated EEG (blue: left; red: right); (e) Left-right spectrogram asymmetry; (f) Rhythmicity right hemisphere; (g) Rhythmicity left hemisphere. All measures present important changes during the four seizures compared to the interictal baseline.

by epileptiform discharges. In five out of the six "false positive" cases, the patient died.

Hermans et al. [11] compared the frequency content of longer time windows, namely one minute before stimulation, and one minute during which the patient underwent a standardized set of auditive and tactile stimuli. Differences in the power spectrum before and during stimulation were judged with five different quantitative measures. Some of these measures were also tested for specific frequency bands. The results of the algorithm were not compared with clinical outcome, but with a consensus made by 3 EEG-specialists. The qEEG measures considering all frequency bands performed better than the ones restricted to specific frequency bands. Interestingly, the methods using specific frequency bands performed differently according to the channels considered. Specifically, lower frequency bands turned out to be accurate in frontal regions, intermediate frequencies in temporal and parietal regions, and faster frequencies were more reliable in occipital regions. In summary, visual inspection remains the gold standard for assessing global EEG reactivity, however, qEEG methods exist that give results in good accordance and allow for band-specific analysis.

QEEG as surrogate encephalographer

Frame-by-frame visual analysis of EEG is time-consuming, especially for long-term ICU continuous monitoring. Several qEEG measures exist that emulate EEG-interpretation by a human electroencephalographer, some of which are even available in commercial software (**Figure 1**). To this end, algorithms have been implemented to detect features that are both salient for the human visual system, and easily programmed on a computer.

One of the simplest features of an EEG signal is its amplitude. Amplitude integrated EEG (aEEG) is a continuous representation of the average peak-to-peak amplitude on a logarithmic scale. Several hours of recording can be represented on a single screen, which can be quickly scanned by clinicians to identify segments of interest that should be reviewed in detail. aEEG has been initially developed for monitoring neonates with post-hypoxic encephalopathy. It has been since then used to predict outcome after cardiac arrest [12] or to detect seizures in the ICU [13].

Another method often considered for computer-assisted EEG interpretation is frequency analysis. A rough estimation of relative power of the different frequency band is used in visual analysis to characterize the background, describe focal slowings or localized attenuations, and even to recognize seizures, which typically display a monotone decrease in frequency and concomitant increase in amplitude. Computers perform frequency analysis with a much higher precision, using for instance the so-called Fast Fourier Transform (FFT). In cases of non-stationary signals such as the ICU EEG, the recording is decomposed into different time-windows on which the FFT is repeatedly computed. The results are then displayed as an array, referred to as spectrogram, or condensed spectrum array (CSA) with time on the horizontal axis, frequency on the vertical axis, and power color-coded. Similarly to aEEG, several hours of EEG recording can be easily visualized in a single plot for electroencephalographers to identify segments of particular interest. In a study on 118 patients admitted for acute illness and undergoing continuous EEG, CSA-guided analysis was performed 4.75 times faster than classical analysis, identified all patients with seizures (though only 87% of seizures), 100% of periodic discharges, 98% of focal slowing and 100% of generalized slowing [13]. This type of analysis has also been validated for seizure detection in pediatric patients in the ICU [14], or in adults by non-EEG expert [15].

Several numerical values can be derived from the power spectrum, such as the absolute power in different frequency bands, or the ratio of power between different frequency bands. Monitoring these values has proven particularly useful in several cerebro-vascular conditions, because of the progressive decrease in dominant EEG frequency in the minutes following a decrease in cerebral blood flow [16]. This approach has been used for instance to monitor vasospasm-induced delayed ischemia after subarachnoid hemorrhage [17]. Changes in total power, in alpha/(delta + theta) power ratio, in relative alpha (i.e. alpha/all frequencies) and relative delta could detect vasospasms even before clinical or neuroradiological signs.

Sharply-contoured transients are also very salient for visual analysis, and can be detected by algorithms. An epileptic spike train detector was mentioned in the previous section; also isolated spikes can be detected. One elegant method is to use wavelet analysis. Wavelets are short oscillating functions of finite durations that can be used as alternatives to windowed FFT for frequency analysis of non-stationary signals. A few studies used sharply contoured wavelets to detect epileptic spikes: the wavelet is moved along the EEG signals, and at places where the two functions fit best, the EEG is likely to contain an epileptic spike [18]. This method has been used in patients in hypothermia after CA for prognostication, and to monitor status epilepticus [19].

Further criteria classically used by electroencephalographers interpreting the EEG of critically ill patients are continuity, regularity, and synchronization between different channels. The Cerebral Recovery Index (CRI) proposed by Tjepkema-Cloostermans et al. [20] incorporates all these features into a single value, which could assist in prediction in the early phase after CA. Five qEEG measures were used: the standard deviation of the amplitude (SD), the alpha-to-delta ratio (ADR), a measure of continuity for detection of burst-suppression patterns (the regularity, REG), a measure of the irregularity of the signal (entropy, H), and finally the coherence in the delta frequency band (COH) as synchronization measure. The five measures were normalized and combined in the following way: CRI = SD*(ADR + REG + H + COH)/4. The rational for multiplying SD with the average of the other four measures was that a non-zero amplitude was required for an EEG to be normal. A low CRI at 24h was associated with an unfavorable outcome, whereas high values were invariably associated with a favorable outcome. As the authors state: "the selection of features was motivated by the EEG characteristics that neurophysiologists evaluate in visual interpretation of the EEG in patients after cardiac arrest".

QEEG as a complement to visual analysis

A 19-channel EEG is a very complex pattern, many properties of which are not easily perceived by humans. Quantitative methods on the other hand can be used to extract parts of this "hidden information", with the hope that it will increase the diagnostic and prognostic yield of EEG.

Non-linear methods are a typical example of measures that humans have little intuition for. Non-linear methods are a set of methods that work well in the study of a particular type of mathematical system (described by a set of non-linear differential equations, hence the name). A detailed presentation of non-linear (vs. linear) methods in EEG analysis can be found in [21]. Here we briefly mention a few: Entropy (which was also already part of the CRI, see above) can be seen as a quantification of the unpredictability for a single event. For instance if a dice has the same number on each face (or: if the EEG voltage is constant at each sampling point), the entropy is low; if a dice has the same probability to give any number from one to six (or: if the amplitude of the EEG can take any value with equal probability), the entropy is maximal. Approximation entropy, or permutation entropy are extensions of the concept of unpredictability to sequences of events (or consecutive sampling point of an EEG channel). These information theoretical measures have been successfully used to differentiate patients in minimal-conscious-state from those in unresponsive-wakefulness-syndrom [22, 23].

Bivariate linear and non-linear measures have been used to compute the synchronization in EEG channels recorded in comatose patients between the left and right parasagittal regions, and between the fronto-central and parietal regions [24]. For each EEG, a total of 8 values were computed (four in the left-right axis, and four in the antero-posterior axis). With these 8 numbers, an EEG could be represented as a single point in an 8-dimensional space. A Bayesian classifier could distinguish regions within this multi-dimensional space containing predominantly EEG from patients who survived, or EEG from patients who deceased during their stay in the ICU. One of the measures also differed according to the etiology of coma.

Classification in a multidimensional space, as performed in the previous example, is called multivariate decoding. This approach can detect information jointly represented by several variables, another property of complex patterns that can be intractable for humans. A series of studies [25, 26] have used multivariate decoding with Bayesian classifiers on multichannel EEGs in a mismatch negativity protocol to predict outcome after CA.

Another type of multivariate information hidden in a multiple channel EEG is the topology of functional networks. Networks can be represented mathematically as graphs. A graph is defined a set of elements (called nodes), and a set of binary connections between pairs of nodes (called links). To construct a graph from a multi-channel EEG, we consider the channels as nodes of the graph, and define links with the help of bivariate measures between the channels. In a study on patients after CA [27], links were defined based on similarity in the power spectrum. The graphs of patients with unfavorable outcome were smaller (less nodes with at least one link), less connected (there were fewer links), and differed in several other graph theoretical properties (such as average shortest path length, cluster coefficient) from graphs derived from patients with normal EEG.

Feature engineering vs. feature learning

In all the methods presented above, the features (frequency, amplitude, entropy, etc.) that are analyzed and then used for interpretation of the EEG have been chosen ahead of time by the programmer, a process called feature engineering. On one hand, this approach makes perfectly sense, since neurophysiologists have acquired a vast knowledge about the meaning of specific EEG features. On the other hand, a potentially extremely useful feature, which no algorithm has been explicitly programmed to detect, might never been used. Feature learning (also called feature extraction, or representation learning) is an approach whereby an algorithm is fed with raw data, and automatically extracts relevant features. Principle component analysis (PCA) and independent component analysis (ICA) are popular feature extraction methods that decompose a signal into decorrelated or independent sub-components, respectively. PCA and ICA can be used on EEG for dimension reduction, artifact eliminations, micro-state definition or source reconstruction. In ICU-EEG analysis, they have been used to measure depths of anesthesia [28] or to identify epochs in coma EEG that should be reviewed by visual analysis [29].

Deep learning methods are a class of methods that have recently been very successful for pattern recognition [30]. In short, deep learning is a set of hierarchical methods, using multiple feature extraction and processing units, organized in layers, whereby the output of one layer is used as input for the next layer. The connections between the different units are adapted in a way that was initially inspired by synaptic plasticity in biological neural systems, in order to optimize specific output. A few studies have already applied deep learning methods to EEG. A four-layer network was used for classification of one-second EEG epochs recorded from critically ill patients into five specified categories (epileptic spike, LPD, blink artefact, GPD/triphasic, continuous background) [31]. The deep learning network operating on raw EEG data had performances similar to other classifiers operating onto a set of 11 hand-coded EEG features (frequency band, line length, wavelet energy etc.), while being faster than the other classifiers when operating on the test set. One interesting property of deep learning networks is unsupervised learning, namely the capability of the algorithms to automatically adjust their internal parameters in order to better identify key features of a signal, without knowing what the correct classification is. This capability reduces the size of the training set needed for supervised learning (where the algorithm is informed if its decision/classification was correct or not). Unsupervised and supervised learning have been used to design a patient-specific seizure detector [32].

Conclusion and outlook

Quantitative methods can be used to analyse EEG recordings in the same way a human would, or, alternatively, to extract "hidden information" that can be used to complement visual analysis in order to increase the diagnostic and prognostic yield. With the possible exception of frequency and amplitude monitoring, these techniques have not yet been incorporated in daily clinical routine. Large prospective studies will be mandatory to confirm the benefit of qEEG in the ICU – alone or in conjunction with other modalities.

In most qEEG studies so far, human programmers have selected by-hand the features to be analyzed, and designed algorithms accordingly. While this approach might still dominate qEEG for the next years, in the future EEG analysis might rely more heavily on automatic feature extraction algorithms, in particular deep learning methods. Deep learning has already proven to be an extremely powerful analysis method and has thus been incorporated in large projects of major technology companies: Facebook uses deep learning for face recognition, Apple for voice recognition in iPhones, Google in its artificial intelligence projects, including AlphaGo, the first algorithm capable of beating professional human Go players [33]. The reasons why deep learning methods have not yet been applied more extensively to EEG analysis are multiple: lack of large enough publicly available collections of EEGs, complex classification categories (interpretation of an EEG only in clinical context) etc.

It is to be expected, however, that large companies will begin to massively invest in deep learning for analyzing diagnostic time series such as EEG. At this point, we will be facing not only technological, but also philosophical and even moral challenges. In deep learning nets, it is often no longer possible to determine which feature was most relevant for pattern recognition. As recently mentioned in an editorial in "Nature" about deep learning: "a human can hardly check its working, or verify its decision before they are followed through (...). The machine becomes an oracle; its pronouncements have to be believed" [34]. Will we entrust an algorithm with the decision to withdraw support to a comatose patient, if we cannot follow the arguments of the decision?

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