Article

Automated Analysis of Background EEG and Reactivity During Therapeutic Hypothermia in Comatose Patients After Cardiac Arrest

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Abstract

Visual analysis of electroencephalography (EEG) background and reactivity during therapeutic hypothermia provides important outcome information, but is time-consuming and not always consistent between reviewers. Automated EEG analysis may help quantify the brain damage. Forty-six comatose patients in therapeutic hypothermia, after cardiac arrest, were included in the study. EEG background was quantified with burst-suppression ratio (BSR) and approximate entropy, both used to monitor anesthesia. Reactivity was detected through change in the power spectrum of signal before and after stimulation. Automatic results obtained almost perfect agreement (discontinuity) to substantial agreement (background reactivity) with a visual score from EEG-certified neurologists. Burst-suppression ratio was more suited to distinguish continuous EEG background from burst-suppression than approximate entropy in this specific population. Automatic EEG background and reactivity measures were significantly related to good and poor outcome. We conclude that quantitative EEG measurements can provide promising information regarding current state of the patient and clinical outcome, but further work is needed before routine application in a clinical setting.

Keywords

electroencephalography, background EEG, reactivity, therapeutic hypothermia, automated analysis

Introduction

EEG monitoring provides important information regarding brain function, particularly in comatose patients,[1-3] and is increasingly used to monitor early changes of cerebral electrophysiology at the bedside in critically ill patients. EEG background activity and EEG reactivity are associated with prognostic information.[2,4-6] Currently, EEG is monitored mostly through visual analysis of the raw signals, but this approach is subjective and therefore dependent on the investigator. Agreement ratings between trained electroencephalographers are generally moderate to good, but not absolute.[7,8] Quantitative EEG analysis, the numerical computations of parameters from the EEG, has received some attention in this setting, and has been shown to offer better validity than visual scoring.[9]

In this specific setting, visually-assessed absent EEG background, lack of reactivity, persistent discontinuous background, or the presence of seizures or epileptiform discharges are strong risk factors of poor outcome[10-13]; these features are generally assessed in normothermia. Recently, EEG reactivity during therapeutic hypothermia (TH) has also been shown to carry robust prognostic information.[2,11,14] Automatic analysis of background EEG has been proposed with methods based on BSR, entropy,[15] or amplitude equivalent EEG[16,17] and shown to have prognostic implications, but was not compared with visual analysis. Furthermore, these studies did not include the important variable of reactivity.

In the present study, we sought to examine the relation between automatic and visual EEG analysis of background EEG and reactivity. We also investigated their prognostic value. Background EEG was analyzed with 2 methods developed to monitor anesthesia: the BSR[18] and the approximate

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entropy.[19,20] Reactivity was analyzed with a method based on frequency features of the signal.

Materials and Methods

Patients

We included 46 postanoxic comatose patients (9 females; age 61 ± 2 years) admitted from January 2011 to May 2012 to the Department of Adult Critical Care Medicine, Centre Hospitalier Universitaire Vaudois (CHUV-Lausanne University Hospital), Lausanne, Switzerland. The study was approved by the ethics committee of the institution. The average time between cardiac arrest and return of spontaneous circulation was 20 ± 12 minutes. Level of consciousness was assessed based on the Glasgow Coma Scale at regular intervals (every 2-3 hours) during the first 48 hours after coma onset. All patients scored 3 or 4 during these first 48 hours, indicating unconscious state.

All patients were managed according to a standard protocol[21]; they were resuscitated following current recommendations (American Heart Association, 2005) and treated with mild therapeutic hypothermia to 33°C for 24 hours, using ice-packs, intravenous ice-cold fluids, and a surface cooling device (Arctic Sun System, Medivance, Luoisville, CO) for the maintenance of therapeutic hypothermia, during which standardized doses of midazolam (0.1 mg/kg/h) and fentanyl (1.5 mg/kg/h) were administered for sedation, and vecuronium (0.1 mg/kg boluses) to control shivering. Patients with myoclonus and/or EEG epileptiform activity were treated with intravenous anti-epileptic drugs, which were discontinued if no clinical improvement was noted after at least 72 hours. An interdisciplinary decision on withdrawal of intensive care support was based on a multimodal approach,[11] including at least 2 of the following (assessed in normothermia at least 48-72 hours after cardiac arrest): incomplete recovery of brainstem reflexes, early myoclonus, bilaterally absent cortical somatosensory-evoked potentials, and lack of EEG reactivity, Specifically, the EEG reactivity during TH, which is the object of the present study, was not used for this decision.

Outcome Assessment

Neurologic outcome was assessed at 3 months by a semistructured phone interview, and categorized according to the Glasgow-Pittsburgh Cerebral Performance Categories (CPC), in which 1 = good recovery, 2 = moderate disability, 3 = severe disability with dependency for daily-life activity, 4 = vegetative state, and 5 = death,[22] and outcome was dichotomized as good (CPC 1 and 2) versus poor (CPC 3 to 5).

Electroencephalography Recording

Video-EEG (Viasys Neurocare, Madison, WI) was performed during TH, by using 19 electrodes arranged according to the International 10-20 System (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, O2) referenced to Oz, ground Fpz, and repeated after rewarming. Background reactivity on EEG was tested with repetitive auditory and nociceptive stimulations performed by a neurologist during and after TH, as described in our previous study.[11] Patients had 5 stimulations on average (range 1-9 stimulations, median 5). While these EEGs were recorded for at least 20 minutes, for the present study, we selected the parts of the recordings that contained stimulations, excluding artifacts, and generated EEG files lasting 3 to 12 minutes. Offline, data were re-referenced to a common average. Some recordings of this data set were previously visually analyzed and the results summarized in a publication.[14]

Visual Scoring

All recordings were interpreted by 2 EEG-certified CHUV neurologists; EEG background reactivity was considered present if cerebral electrical activity of at least 10 μV (regardless of frequency range) was observed, and EEG background showed any clear and reproducible change in amplitude or frequency on simulation (auditory or painful), excluding "stimulus-induced rhythmic, periodic, or irritative discharges" (SIRPIDS)[23] or induction of muscle artifact alone. Stimulation and EEG background activity were assessed in all patients at least 12 hours after the start of TH (ie, during the maintenance phase of TH) and within 24 hours from cardiac arrest, still during TH. EEG background interrupted by flat periods lasting more than 10% of the recording was labeled as "discontinuous"[24] if this pattern was found over the whole recording. Spontaneous, repetitive or rhythmic, focal or generalized spikes, sharp waves, spike and waves, or rhythmic waves evolving in amplitude, frequency, or field were categorized as "epileptiform," as detailed in our previous studies.[11,25,26] Of note, no patient presented isolated epileptiform transients. After reviewing the EEG separately, the 2 EEG-certified neurologists established a consensus score.

Automatic Analysis

In the current study, automatic processing of the data described background activity and reactivity to auditory or nociceptive stimulation (reactive/not reactive). Background activity was automatically measured by computing the BSR[18] and the approximate entropy[19] on Fz, Cz, and Pz. In the BSR, suppression intervals are defined as periods longer than 240 ms during which EEG voltage does not exceed 5 μV.[18] BSR represents the ratio between the total suppression time and the total recording time. An EEG was considered suppressed if the ratio was greater than a chosen threshold.

Approximate entropy is a measure that quantifies the regularity or predictability of a time series. Approximate entropy has been applied to the analysis of EEG to measure depth of anesthesia[20,27] or to estimate sleep stage,[28] and was shown to correlate with BSR during anesthesia.[29] Approximate entropy measures the logarithmic likelihood that runs of patterns that are close for *m* contiguous observations remain close on subsequent

comparisons between $m + 1$ contiguous observations. Approximate entropy is a relative measure, which depends on 3 parameters: the number of contiguous observations m, the length of the epoch N, and a distance measure r.[19,30] In our analysis, we used $m = 2$ and 8-second epochs ($N = 2000$), based on theoretical considerations[19,30] and previous studies.[20,27] These studies also suggested choosing $r = 0.1$, 0.15, 0.2, or 0.25 times the standard deviation of the original data sequence. The present data had standard deviation ranging from 0.8 to 17.3 (mean = 5.5 ± 3.3). As comparisons between time series segments can only be made with the same values of m and r, and Bruhn and colleagues[29] in a study on approximate entropy and BSR suggested not to use a standard deviation below 7, we decided to take $r = 0.2*7$ for all data.

Reactivity to stimulation was computed as change in power at given frequencies between two 1-second windows taken half a second before and after stimulation (Figure 1). Data were high-pass filtered above 1 Hz before they were epoched. The Welch periodogram algorithm estimated the power spectrum of each 1-second window. The frequencies of interest were selected as the peaks in the power spectrum. A peak has to be at least as high as 20% of the maximum value in the window to be recognized as a peak. A stimulation was considered reactive if (*a*) a peak detected at a given frequency was twice higher than same frequency of the other window[31], and (*b*) a peak was also present and twice higher on a chosen minimal number (see below) of other electrodes. The reactive frequency ±0.5 Hz was checked in other conditions. The frequency with most reactive conditions was kept. The final result was the ratio between the number of detected change and the total number of stimulations in a recording. To avoid false positive results due to change in activity not related to stimulation, we removed from analysis the windows fulfilling 1 of the 2 following criteria. First, the number of detected peaks was greater than a maximum number (see below). This corresponds to the fact that no clear peak appears in these data. Second, the change in total power between pre- and post-windows was greater than a threshold (see below). High change of the whole spectrum was most probably due to pathological EEG patterns, such as epileptiform bursts on a suppressed background.

Comparison Between Automatic and EEG-Certified Neurologists

To compare the ratio of automatic scoring with the binary EEG-certified neurologist scores, we fixed a threshold at 0.5. A recording was reactive if at least half of the stimulations were reactive. We computed the agreement between automatic detection of reactivity and the reactivity given by the consensus score. We also computed Cohen's κ coefficient, which takes into account sensitivity, specificity and agreement occurring by chance.

The choice of parameters (minimum number of electrodes to name a condition reactive, maximum number of peak in the power spectrum, threshold on the total power) had an influence on the final results: with strict parameters, we may reject as noise reactive stimulations. On the other hand, with loose parameters, every artifact may induce false reactivity. Therefore, parameter selection was done through an approach from machine learning, a 9-fold cross-validation scheme. The 46 subjects were randomly distributed into 9 sets (8 sets of 5 subjects and one of 6 subjects). We then repetitively performed an exhaustive search for best parameters on 8 sets and applied these parameters to the remaining set. Each patient was then used once as a test subject with parameters independently selected. We repeated this procedure 5 times with different folds and averaged the final results. During exhaustive search, we optimized Cohen's κ coefficient between automatic measure and consensus score.

Third Reviewer

The EEG was further reviewed by a separate third EEG neurologist, from Liège, who did not have access to patients' medical information. This third reviewing was intended as a comparison with the automatic score in similar condition (only short EEG segment). We computed the agreement and Cohen's κ coefficient between the score from the third neurologist and the clinical consensus score of the CHUV neurologists.

Results

The clinical characteristics of the 46 patients are summarized in Table 1. At 3 months, 25 of the 26 patients, who left the hospital alive, were assessed: 21 had a CPC of 1 or 2 (good outcome), while 3 had a CPC of 3, and 1 patient died; 1 patient was missed. The remaining patients died in hospital. Of note, no patient remained in a vegetative state. Visually, the CHUV neurologists considered that 1/21 patients with good outcome, and 15/24 with poor outcome, had a nonreactive EEG background in hypothermia, while corresponding proportions for a discontinuous background were 4/21 and 23/24.

Quantitative results were compared to the consensus score of the 2 CHUV neurologists. The receiver operating characteristic curves of agreement between automatic and consensus score of background activity are presented in Figure 2. Automatic analysis of background activity on Fz yielded 93.5% correspondence with the background activity of the consensus score ($\kappa = 0.86$; almost perfect agreement) with a threshold of 0.12. Similar agreements were obtained for Cz and Pz (89.1% for Cz, and 91.3% for Pz). Approximate entropy negatively correlated with BSR ($r = -0.76$, -0.77, and -0.78 for Fz, Cz, and Pz, respectively, $P < .001$; Figure 3). The correspondence between consensus score and approximate entropy was lower than for BSR on all electrodes. The computation of approximate entropy on Fz yielded 82.6% correspondence with background activity of consensus score ($\kappa = 0.64$) with a threshold of 0.55.

The automatic procedure for reactivity had 79% ± 2% ($\kappa = 0.71 \pm 0.01$) agreement (substantial) with the consensus score (Figure 1). One combination of parameters was selected the majority of the time. In that combination, the minimum

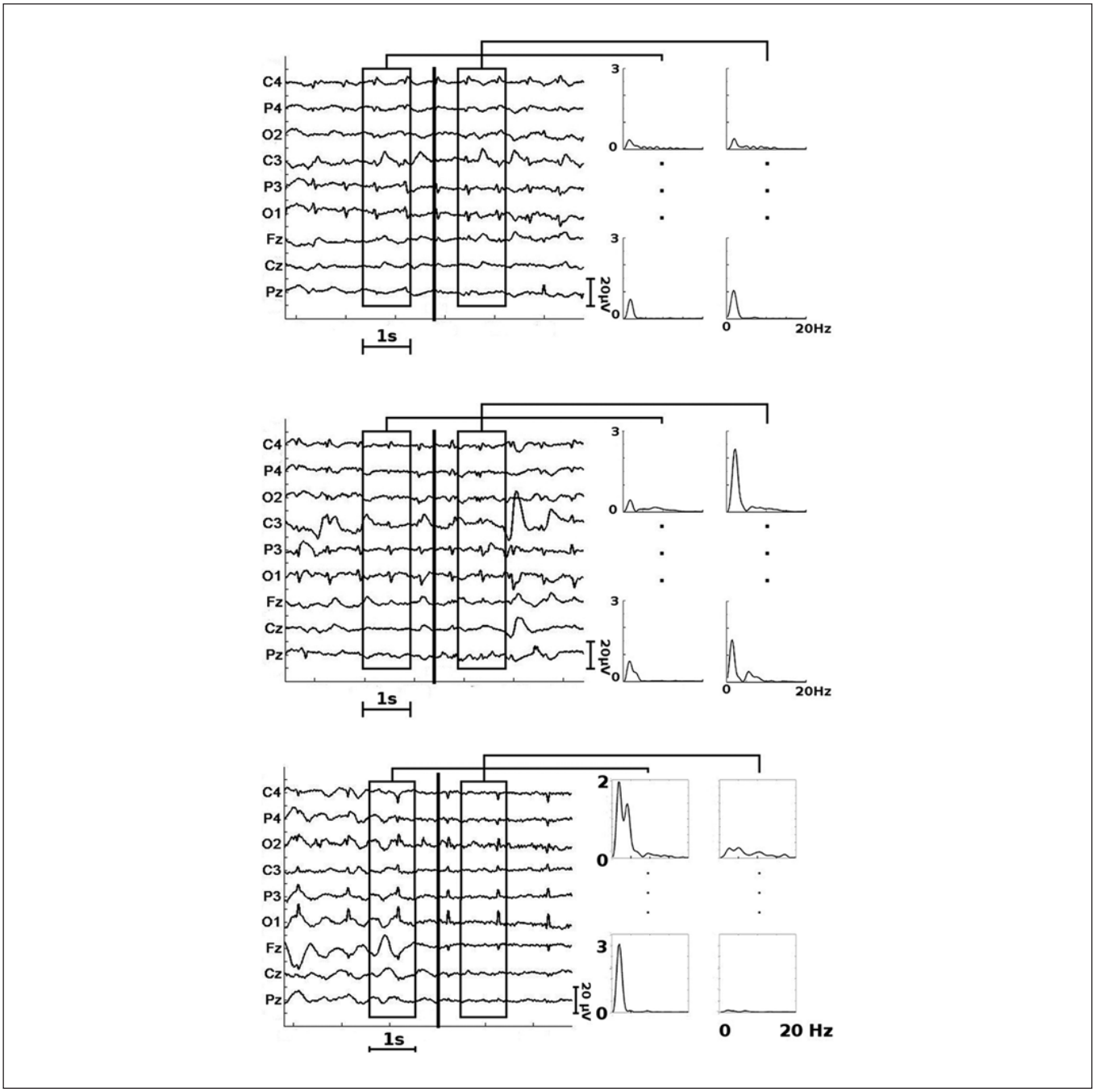

Figure 1. Computation of reactivity. (Left) A subset of the original EEG. The black vertical line indicates the stimulation. The two 1-second windows are taken half a second before and after stimulation. (Right) The power spectrum decomposition of the one-second windows before and after stimulation. One electrode by row. First figure, a stimulation where no change is detected, neither by the physicians nor by the automatic scoring. Second figure, a stimulation which is considered as reactive by the automatic scoring (increased low frequency) and as nonreactive by the physicians. Third figure, a stimulation inducing a decrease of low frequency as detected by physicians and automatic scoring.

number of electrodes to name a condition as reactive was 6, the maximum accepted number of peak in the power spectrum was 4, and the threshold on the total power was a ratio of maximum 5 between the total power before and after the stimulus. Other combinations were slight variations of the favored combination.

Six subjects were reactive in the 5 cross-validations while the clinical assessment diagnosed them as non-reactive. One subject was automatically diagnosed as non-reactive while clinically considered as reactive. One more subject was automatically diagnosed as non-reactive 4 times out of 5. A few other subjects were selected as reactive or non-reactive once or

Table 1. Clinical characteristics of the studied patients.

	Good Outcome (21 Patients)	Poor Outcome (24 Patients)
Age in years, mean ± SD)	60.1 ± 11.2	63.1 ± 12.4
Female gender, n	4	5
Ventricular fibrillation, n	14	14
Time to return of spontaneous circulation in minutes, mean ± SD	18.8 ± 13.0	21.5 ± 10.4
Mean delay from cardiac arrest to EEG recording of stimulations during hypothermia in hours, mean ± SD	17.4 ± 6.5	20.0 ± 5.8
Hypotermic EEG epileptiform, n	0	5
Bilaterally absent somtosensory-evoked potentials, n	0/21	9/23
Cerebral performance categories at 3 months, median (range)	1 (1-2)	5 (3-5)

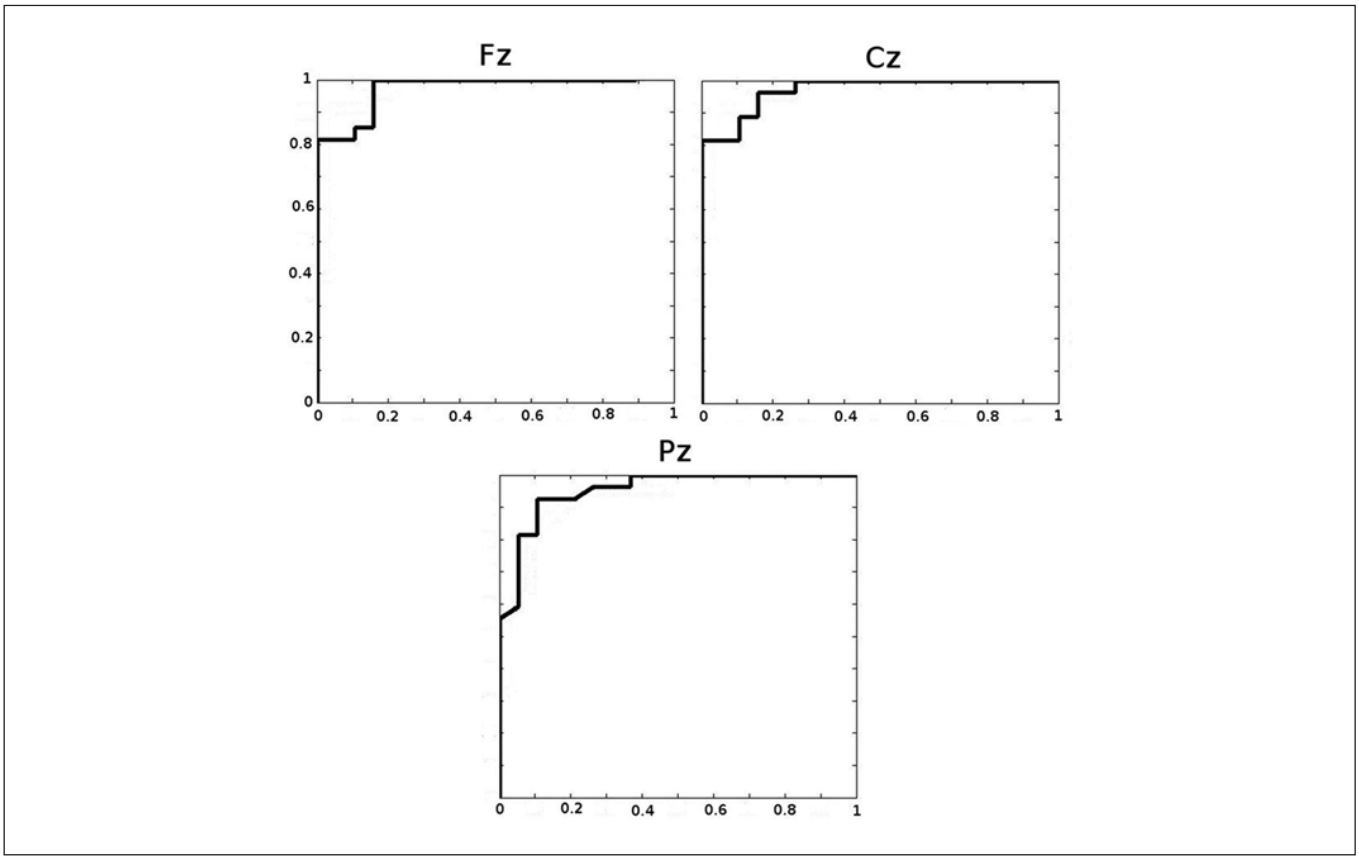

Figure 2. Receiver operating characteristic (ROC) curves of BSR and physicians' EEG continuity scores for electrodes Fz, Cz, and Pz.

twice, while consensus clinical score had the opposite diagnosis.

The association between outcome and EEG findings from the consensus score and the automatic score during TH is shown in Table 2. Non-reactive EEG background and discontinuous EEG background were strongly associated with poor outcome by both consensus and automatic scores. Continuous EEG background was associated with a good outcome. The average BSR was significantly lower in the good outcome group than in the poor outcome group for all electrodes (permutation test, 10 000 permutations; Table 3). The approximate entropy values were significantly higher in the good outcome group than in the poor outcome group (permutation test, 10 000 permutations; Table 3).

The third physician score achieved a 91.3% agreement on the background activity ($\kappa = 0.83$) with the consensus score and a 78.3% agreement on the reactivity ($\kappa = 0.53$).

Discussion

In the present study, automatic analysis of background activity and reactivity in patients in TH following cardiac arrest provided results almost perfect in agreement with visual inspection by certified EEG neurologists regarding discontinuity, and

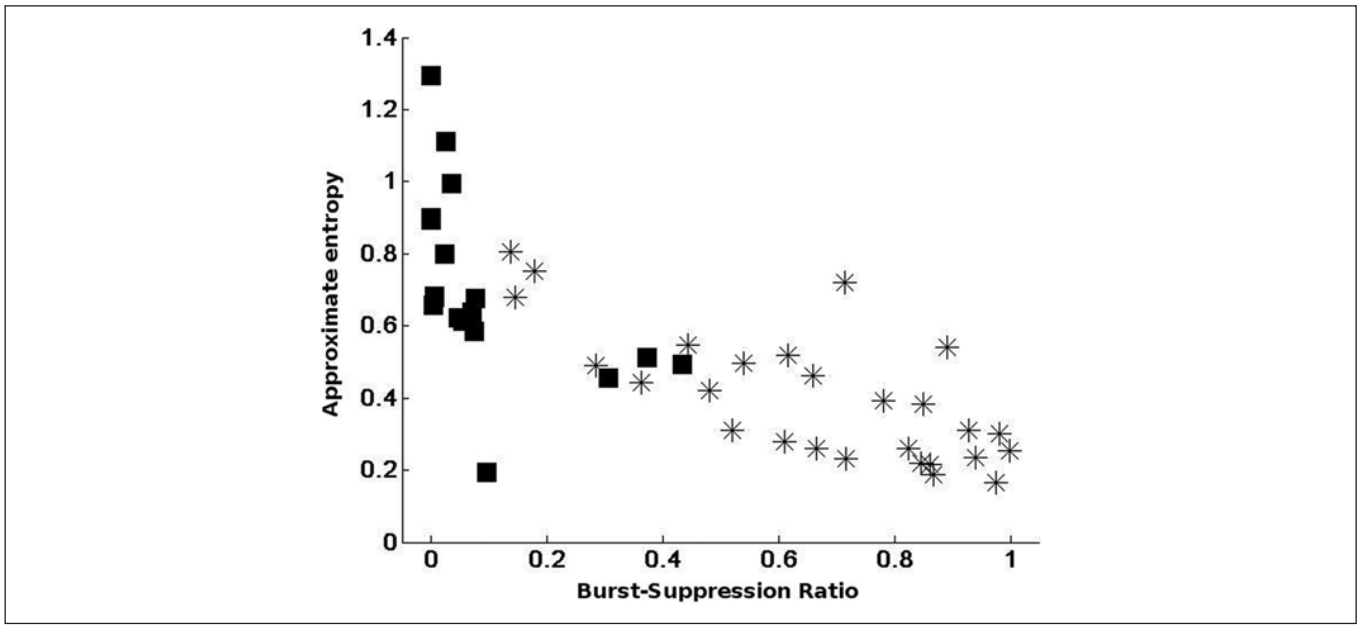

Figure 3. Correlation between BSR and approximate entropy for Fz. Squares correspond to patients with continuous background following the clinical EEG interpretation. Stars correspond to patients with discontinuous background .

Table 2. Automatic Score in Good Outcome and Poor Outcome Groups.

	Good Outcome (n = 21)	Poor Outcome (n = 24)	*P* Value From Fisher's Exact Test
Non-reactive cEEG background, n (%)			
Clinical score	1 (5)	15 (63)	<.01
Automatic score	2 (10)	10 (42)	<.01
Discontinuous background activity ("burst-suppression"), n (%)			
Clinical score	4 (19)	23 (96)	<.01
Automatic score	6 (29)	24 (100)	<.01

Table 3. Average and Median Values of Burst-Suppression Ratio (BSR) and Approximate Entropy (Apen) for Good Outcome and Poor Outcome Groups.

	Good Outcome		Bad Outcome		
	Mean	Median (25-75 Quintiles)	Mean	Median (25-75 Quintiles)	*P* Value
BSR					
Fz	0.18	0.07 (0.02-0.19)	0.70	0.69 (0.46-0.86)	<.01
Cz	0.26	0.16 (0.05-0.42)	0.70	0.69 (0.54-0.91)	<.01
Pz	0.31	0.20 (0.12-0.38)	0.72	0.71 (0.61-0.88)	<.01
Apen					
Fz	0.65	0.64 (0.48-0.71)	0.41	0.41 (0.25-0.52)	<.01
Cz	0.58	0.58 (0.40-0.67)	0.38	0.39 (0.21-0.49)	<.01
Pz	0.57	0.56 (0.37-0.70)	0.38	0.34 (0.18-0.58)	<.01

substantial agreement regarding EEG reactivity; agreements were comparable to the observed inter-rater agreement among clinicians. The automatic scoring was also a good predictor of outcome.

Clinical EEG analysis in the intensive care unit is mostly based on visual inspection of the raw signal to detect background patterns, epileptical activities, and reactivity. This approach is time consuming and requires extensive training.[31]

Quantitative EEG analysis can provide complementary information and improve generalizability.

Reactivity is defined as change in cerebral EEG activity in response to stimulation[24]; however, formal guidelines do not exist. Lack of reactivity is related to poor neurologic recovery[4,5]. In patients with postanoxic coma, non-reactive EEG background activity during or after TH is an early predictor of poor outcome.[2,6] Previous automatic detection of reactivity was limited to data from patients investigated for epilepsy and the detection of attenuation of the alpha band over the occipital region between an idle and an eye-open state.[31] The present approach is wider, investigating more types of stimulations, more frequency bands, and more electrodes. The proposed automatic approach to detect reactivity was in good agreement with the consensus scores. However, 7 patients obtained an automatic score different from the consensus score. The automatic approach did not detect any reproducible change, while the consensus score detected reactivity in the theta band in 1 patient. This patient had a good outcome. In 6 patients, the automatic score found reactive patterns but not the consensus score: 2 patients presented a high-voltage burst-suppression just before or after stimulations, 2 had a slight increase in delta activity following stimulations, and another patient had epileptiform activity. All these patients died. One last patient presented changes in delta activity in half of the stimulations; despite being scored as non-reactive by the consensus score, he had a good outcome.

The proposed approach scored each stimulation individually before testing the interstimulation reproducibility. If reproducibility is important, ideally it should be compared among stimulations of the same intensity. A patient may not respond to auditory stimuli but to pain, in which case the neurologist will classify the EEG as reactive, while the automatic scoring will consider that only one-third of the stimulations are reactive. This scenario was not present in our data, but it illustrates the difficulty to reduce a classification for each stimulation to a binary score for the whole recording. Furthermore, the number of stimulations varied from one subject to the next, and the response to previous stimulations as well as other clinical factors may influence the decision to continue or stop the test. To enable the comparison between automatic scores and consensus scores, we set an arbitrary threshold at 0.5. Half of the stimulations had to be reactive in order to score a recording reactive. In future developments, an individual score should be given for each stimulation as well as group of stimulations, which could reflect the intensity of the reaction.

BSR and entropy measures have been developed for anesthesia before being applied to comatose patients.[15,32] The BSR and entropy characteristics have significantly different values in good outcome and poor outcome groups[15], as confirmed in the present study. Discontinuous EEG background is strongly associated with poor outcome,[6,11,14] although (in clinical EEG interpretation) it is less robust than lack of background reactivity. Furthermore, we tested the agreement between automatic and physician score. A high or low BSR was an unequivocal sign of discontinuous or diffuse continuous background, respectively. Patients with in-between values (from 0.1 to 0.5 for frontal lead) should be further inspected by EEG-certified neurologists to disentangle discontinuous background from other patterns. The consensus score differed from the score of the third physician for 3 of the 10 patients in this "gray zone." Three more patients had a BSR above the threshold, while both physicians classified their EEG as continuous. Indeed, on visual inspection these patients had an EEG with very low power but no sign of discontinuity. One of these 3 patients died after leaving the hospital while the other 2 had a good outcome. One patient suffered from epilepsy, which increased his BSR. The remaining 3 patients were scored identically by physicians and BSR.

Approximate entropy was shown to be negatively correlated with the BSR, but less sensitive than BSR with regard to consensus score. The negative correlation is in accordance with results from anesthetized subjects, where approximate entropy was inversely related to BSR ($r = -0.94$).[27] Approximate entropy measures the complexity of the signal and has been shown to correlate with the level of anesthesia[20,27,29] or sleep. EEG entropy was shown to correlate with the coma recovery scale in an acute setting.[32] Further studies are needed to see if approximate entropy may be more suited to follow longitudinally a given patient, or rather to disentangle background patterns or rhythms.

Automatic scoring is sensitive to epileptiform activity, muscle activity, and other artifacts. One patient had generalized periodic discharges with a suppressed background and no sign of reactivity, according to the three neurologists. Both BSR and approximate entropy could not detect the suppressed state which should have resulted in a high BSR and low approximate entropy. Instead, the BSR was at the border with continuous background and the entropy was in the middle range. Furthermore, the subject was scored reactive. The present approach was not developed to detect epileptiform activity as only 2 recordings in our cohort presented epileptical activity. Of note, approaches based on wavelet entropy[15] or amplitude-integrated EEG[16] have been proposed to automatically detect epilepsy in comatose patients.

Quantitative EEG provides results in accordance with trained physicians' scoring, but the correlation is not absolute. Pending confirmation in a larger data set and the identification of reliable thresholds (especially for entropy), we propose that this quantitative EEG analysis might contribute to improving the generalization of EEG interpretation in this clinical setting and provide an objective baseline for prognosis and research.

Declaration of Conflicting Interests

The authors declared no conflicts of interest with respect to the research, authorship, and/or publication of this article.

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