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Short paper

Electroencephalography-based power spectra allow coma outcome prediction within 24 h of cardiac arrest

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Abstract

Background: Outcome prediction in comatose patients following cardiac arrest remains challenging. Here, we assess the predictive performance of electroencephalography-based power spectra within 24 h from coma onset.

Methods: We acquired electroencephalography (EEG) from comatose patients ($n = 138$) on the first day of coma in four hospital sites in Switzerland. Outcome was categorised as favourable or unfavourable based on the best state within three months. Data were split in training and test sets. We evaluated the predictive performance of EEG power spectra for long term outcome and its added value to standard clinical tests.

Results: Out of 138 patients, 80 had a favourable outcome. Power spectra comparison between favourable and unfavourable outcome in the training set yielded significant differences at 5.2–13.2 Hz and above 21 Hz. Outcome prediction based on power at 5.2–13.2 Hz was accurate in training and test sets. Overall, power spectra predicted patients' outcome with maximum specificity and positive predictive value: 1.00 (95% with CI: 0.94–1.00 and 0.89–1.00, respectively). The combination of power spectra and reactivity yielded better accuracy and sensitivity (0.81, 95% CI: 0.71–0.89) than prediction based on power spectra alone.

Conclusions: On the first day of coma following cardiac arrest, low power spectra values around 10 Hz, typically linked to impaired cortico-thalamic structural connections, are highly specific of unfavourable outcome. Peaks in this frequency range can predict long-term outcome.

Keywords: Coma, Consciousness, EEG

Introduction

Currently, prognostication of comatose patients' outcome after cardiac arrest (CA) relies on multimodal testing, combining results of clinical examinations, electrophysiological tests, neuroimaging and biomarkers.[1] Some EEG patterns are predictive of poor outcome,[2,3] whereas early, continuous EEG[4] and evidence of EEG-based response to painful stimulation can predict good outcome.[5] EEG pattern evaluation requires specific expertise and can suffer from inter-rater variability.[6] Other reports document that up to 20% of decisions to withdraw life-supporting therapies within 72 h of CA might

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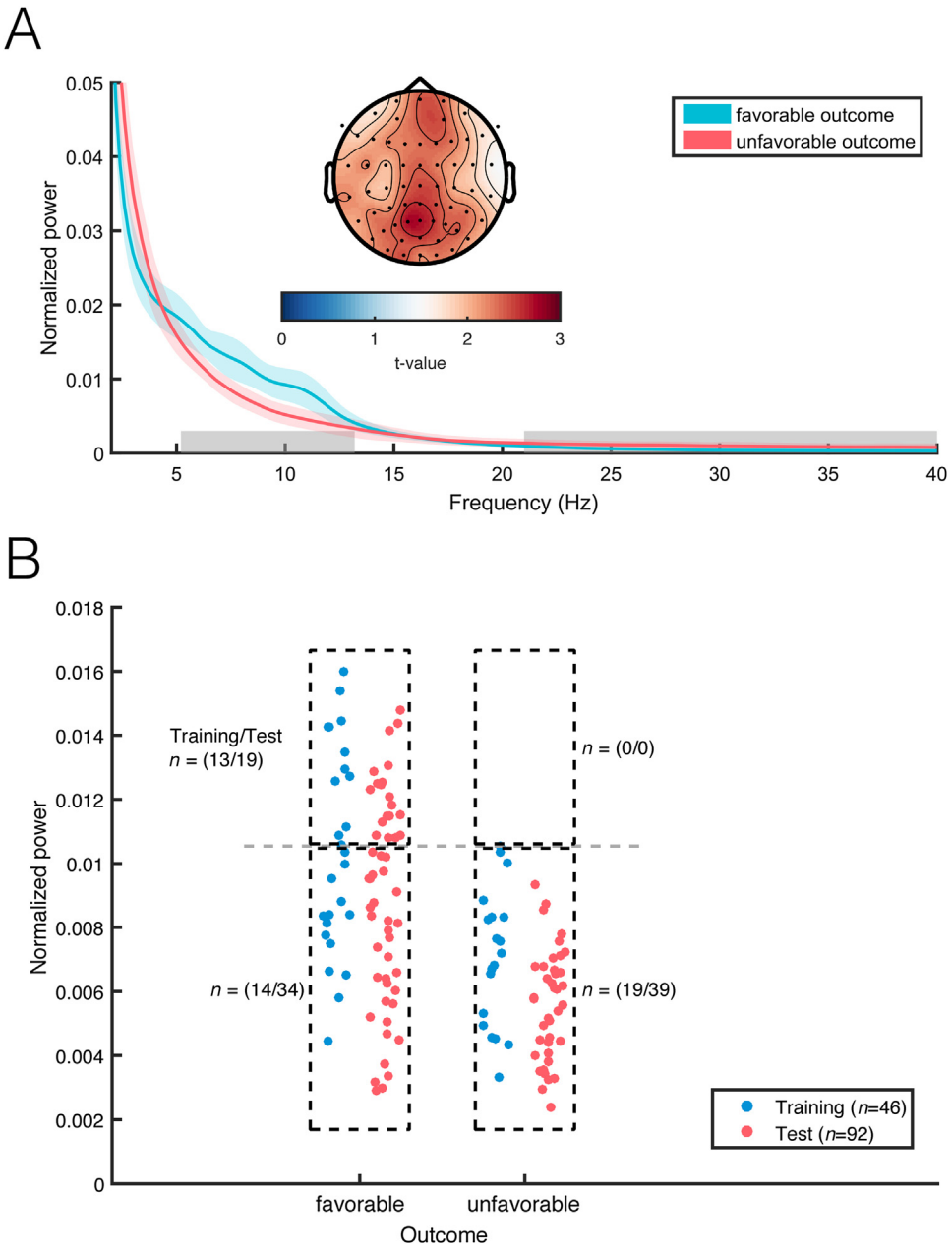

Fig. 1 – (A) Power spectra in arbitrary units for FO and UO. Grey bars highlight frequencies at which we found statistically significant differences (5.2–13.2 Hz and above 21 Hz). Topographical inset reflects t-values of differences between the two groups (all electrodes significant). (B) Outcome prediction based on normalized spectral power in arbitrary units. Blue and red dots refer to patients in the training and test sets respectively. The horizontal dashed line indicates the prediction threshold for outcome prediction. In parentheses, the two values refer to training and test sets in each subgroup. Across the whole dataset, we correctly predicted FO in 32 patients without false positives. (For interpretation of the references to color in the text, the reader is referred to the web version of this article.)

reflect a misdiagnosis.[7] These limitations encourage the development of quantitative markers of patients' long-term outcome, i.e. by quantifying the evoked response from auditory stimuli[8,9] or by characterising features of the neural activity at rest.[10] In this new study, we capitalize on evidence that disorders of consciousness are associated to functional impairments of cortico-thalamic connections and associated with specific EEG power spectra features.[11] To the best of our knowledge, no studies provided quantitative estimations of EEG power spectra predictive performance for long-term outcome during early stages of coma. Here, we analyse the prognostic value of the EEG power spectra during the first day of coma in comatose patients.

Materials and methods

Post-anoxic comatose patients

Electroencephalography was prospectively recorded from 138 comatose patients after CA on the first day of coma at the intensive care units of the University Hospitals of Lausanne ($n=68$), Sion ($n=5$), Fribourg ($n=2$) and Bern ($n=63$) in Switzerland between July 2014 and January 2018. The study was approved by the ethics committees of the respective institutions (PB_2016-00530 (23/05)). Prior to any recording, written informed consent was signed by a family member, legal representative, or treating clinician not involved in this study. Patients received targeted temperature treatment at either 33 °C ($n=18$), at 36 °C ($n=115$) or no intervention ($n=5$), including continuous infusion and bolus injections of sedative agents during the first 24 h after CA.[1] Patient's functional and neurological condition was assessed using the Full Outline of UnResponsiveness Score (FOUR[12]).

Patient's outcome was defined according to the best functional outcome within three months post CA, considering the Cerebral Performance Categories (CPC[13])– a semi-structured phone interview at three months after CA – and the neurological examination during hospitalization. Patients scoring a CPC of 1–2 at any point in time during the first three months after cardiac arrest were considered patients with favourable outcome (FO), the rest were considered patients with unfavourable outcome (UO).

Clinical assessments

A certified neurologist assessed pupillary, oculocephalic and corneal reflexes, motor reactivity to pain stimulation and background reactivity based on bedside EEG recordings.[5] Bilateral median nerve somatosensory evoked potentials evaluation was carried out within 24–48 h of CA. Withdrawal of care was decided based on a multidisciplinary approach[1] and – for patients in Bern – additionally on the concomitant presence of major hypoxic/ischemic lesions in structural magnetic resonance imaging and neuron-specific enolase levels more than twice above 33 μg/l.[14] Clinical decisions were blinded to the results of the EEG power spectra analysis.

EEG methods

Acquisition and preprocessing

We recorded resting EEG for 8–20 min using a 63 active ring electrode array (g.HIamp, g.tec medical engineering, Graz, Austria) in the 10–10 system at 1200 Hz, referencing to the right ear lobe. Additional electrodes were attached to the patient's chest to record electrocardiography. The EEG data were segmented into 5 s epochs and downsampled to 500 Hz. Based on an independent component analysis,[15] we removed components containing identifiable electrocardiographic signal. We interpolated artifacted electrodes and applied average reference. The number of epochs did not differ between FO and UO (mean and standard deviation indicated, n_{FO}: 178.74 ± 36.65, n_{UO}: 173.53 ± 37.45, $t(136) = 0.82$, $p = 0.42$) while the number of interpolated electrodes was overall low, but higher in patients with UO (n_{FO}: 0.79 ± 1.61, n_{UO}: 1.72 ± 2.82, $t(136) = -2.48$, $p = 0.02$).

EEG analysis

For each patient, we computed the power spectra in each epoch and electrode for 2–40 Hz in 0.2 Hz steps based on nine Slepian tapers for 1 Hz smoothing. We then averaged the power spectra across epochs and normalised the results based on the sum of all spectral values. Using only data from the training set, we compared the average power spectra between FO and UO at group-level using a cluster permutation test[16] with 5000 permutations and a two-sided cut-off at $p < 0.05$. For the prediction analysis, we computed the average of the spectral values across a cluster of frequencies and electrodes at which we observed statistical differences at group-level. This resulted in one power spectral value for each recording. We then estimated an optimal threshold within the range of spectral values across all recordings in the training set to maximise the PPV with at least ten predicted patients with FO. For validation, we assessed the outcome prediction in the test set using the same frequencies and spectral value threshold as in the training set.

Results

Patient characteristics

Within the 138 patients, 80 had FO. The average FOUR score of FO was 4.69 ± 0.38 whereas UO scored 2.4 ± 0.30. The whole EEG dataset was split into training ($n_{FO} = 27$, $n_{UO} = 19$) and test ($n_{FO} = 53$, $n_{UO} = 39$) sets.

Power spectra analyses and outcome prediction

In the training significant statistical differences in the spectral power of FO and UO ($p = 0.02$) occurred at 5.2–13.2 Hz and above 21 Hz across all electrodes (Fig. 1A). In the training set, we extracted the average spectral value along 5.2–13.2 Hz, based on our group-level analysis and a previous report on its neurophysiological relevance[11] (see Supplemental Fig. 1 for individual spectra). After optimising the spectral value threshold for outcome prediction, we correctly predicted 13 patients with FO without false positives (PPV: 1.00; CI: 0.75–1.00, Fig. 1B, blue dots). A lower than threshold power spectral value turned out to be highly specific for UO (specificity: 1.00, CI: 0.82–1.00). These results were confirmed in the test set (PPV: 1.00; CI: 0.82–1.00 and specificity: 1.00; CI: 0.91–1.00; Fig. 1B, red dots).

Clinical characteristics and outcome prediction

We compared the clinical characteristics of patients with FO falling above and below the spectral power threshold using

t-statistic and Fisher's exact test in order to exclude that clinical differences could explain the prediction results. We found no significant differences with respect to medication and the majority of patients' characteristics (Table 1). By investigating the predictive value of the EEG continuity, the reactivity and their combination with the spectral power, we found that the EEG spectral power alone provided the best results in terms of specificity and PPV, whereas the combination of reactivity and spectral power yielded the highest sensitivity and accuracy (Table 2).

Discussion

We investigated the spectral properties of post CA coma patients during the first day of coma and their relation to patients' outcome. The average spectral power between 5.2 and 13.2 Hz was highly specific for UO and accurately predicted FO in comatose patients after CA in a cohort of 138 patients within 24 h of coma onset. This quantitative marker complemented existing EEG based prognosticators, especially reactivity. Our results are consistent with a

Table 1 – Characteristics of patients with FO according to the prediction results. Demographic and clinical comparisons of FO above and below the power spectra based prediction threshold; *n* refers to the number of patients on which the statistic is computed and $n_{missing}$ refers to the number of missing values respectively. FOUR score based on data available for composite and sub-scores (*n* = 71 and *n* = 49, respectively). Statistical results are shown based on t-statistic or Fisher's exact test. As there were no false positive predictions, the comparisons were not performed for UO. ROSC = Return of spontaneous circulation; *M* = mean; *SD* = standard deviation; *OR* = odds ratio.

	Power spectra		
	Above threshold	Below threshold	p-Value
Favorable outcome			
N	32	48	
ROSC (minutes), $M \pm SD$	20.65 ± 13.63	17.74 ± 12.76	0.35
Age (years), $M \pm SD$	58.81 ± 15.34	65.70 ± 12.12	0.04
Time to EEG (h), $M \pm SD$	19.50 ± 5.55	21.01 ± 6.00	0.27
Temperature (Celsius), $M \pm SD$	35.70 ± 0.90	35.59 ± 1.20	0.64
Propofol (mg/kg/h), $M \pm SD$ (*n*)	2.56 ± 1.43 (23)	2.60 ± 0.91 (35)	0.91
Midazolam (mg/kg/h), $M \pm SD$ (*n*)	0.13 ± 0.05 (10)	0.12 ± 0.06 (19)	0.45
Fentanyl (µg/kh/h), $M \pm SD$ (*n*)	1.04 ± 0.94 (24)	1.31 ± 1.17 (33)	0.36
FOUR, $M \pm SD$	4.79 ± 2.51	3.26 ± 2.20	0.06
Eye, $M \pm SD$	0.00 ± 0.00	0.03 ± 0.16	0.32
Motor, $M \pm SD$	0.56 ± 1.07	0.40 ± 0.97	0.71
Brainstem, $M \pm SD$	2.88 ± 1.00	2.36 ± 1.37	0.23
Respiratory, $M \pm SD$	0.44 ± 0.50	0.68 ± 0.47	0.25
Gender (male), *n* ($n_{missing}$)	30 (0)	37 (0)	0.07
EEG reactivity, *n* ($n_{missing}$)	5 (5)	7 (8)	1
EEG discontinuity, *n* ($n_{missing}$)	5 (1)	21 (1)	<0.01
Electrographic epileptic activity, *n* ($n_{missing}$)	1 (1)	0 (1)	0.40
Pulmonary etiology of CA, *n* ($n_{missing}$)	5 (0)	8 (1)	1
Pupillary reflexes, *n* ($n_{missing}$)	27 (5)	36 (9)	0.26
Corneal reflexes, *n* ($n_{missing}$)	24 (5)	32 (10)	0.72
Motor response, *n* ($n_{missing}$)	22 (5)	26 (9)	0.26

Table 2 – Summary of outcome prediction. Prediction results for FO based on the power spectra, continuity of the EEG and EEG reactivity, separately and combined. Here training and test sets are merged. 95% confidence intervals in parentheses. Highest overall PPV provided by spectral power while a combination of spectral power and reactivity of the EEG yielded the most accurate predictions.

Predictor	TP/FP/FN/TN	PPV	NPV	Sensitivity	Specificity	Accuracy
Power spectra (5.2–13.2 Hz)	32/0/48/58	1.00 (0.89–1.00)	0.55 (0.45–0.64)	0.40 (0.29–0.52)	1.00 (0.94–1.00)	0.65 (0.57–0.73)
EEG continuity	52/9/28/49	0.85 (0.74–0.93)	0.64 (0.52–0.74)	0.65 (0.54–0.75)	0.85 (0.72–0.93)	0.73 (0.65–0.80)
Combination of spectral power & EEG continuity	58/9/22/49	0.87 (0.76–0.94)	0.69 (0.57–0.80)	0.73 (0.61–0.82)	0.85 (0.75–0.94)	0.78 (0.70–0.84)
EEG reactivity	55/7/25/51	0.89 (0.78–0.95)	0.67 (0.55–0.78)	0.69 (0.57–0.79)	0.88 (0.77–0.95)	0.77 (0.69–0.8)
Combination of spectral power & EEG reactivity	65/7/15/51	0.90 (0.81–0.93)	0.77 (0.65–0.87)	0.81 (0.71–0.89)	0.88 (0.77–0.95)	0.84 (0.77–0.90)

previous report where in traumatic brain injury patients, alpha power negatively correlated with the degree of atrophy in the dorsal and ventral thalamus over months and predicted functional recovery.[17] Previous studies found prominent alpha peaks in disorders of consciousness patients emerging from minimally conscious state and in none of the comatose patients.[11] Differences in the latency from coma onset, the effect of sedation and of the targeted temperature management in our cohort provide possible explanations for this divergence. The sedative medication on the first day after CA might have probed networks underlying the generation of alpha oscillations (Fig. 1 and Supplemental Fig. 1), thus uncovering power spectra reflecting preserved cortical integrity. As current guidelines recommend clinical decisions to withdraw life support after 72 h post incident or temperature treatment,[18] timely prognostication provided by power spectra during the first day of coma could turn out to be highly relevant for clinical practice.

The power spectra-based prognostication overlaps strongly with the EEG continuity. Although the presence or absence of the alpha rhythm in the EEG, one of the most prominent rhythms in the human brain, is certainly linked to the continuity of the signal, their correspondence is not straightforward as continuity itself is defined by signal amplitude rather than frequency.[19] The combination of power spectra and continuity outperform the prediction based on each of the two metrics alone, confirming a non-trivial overlap.

Outcome prediction based on EEG power spectra is a new quantitative and easy-to-implement approach, which may aid prevention of inappropriate withdrawal of life support decisions in cases of uncertain outcome.

Future studies will investigate the functional role of alpha band activity in comatose patients by investigating functional connectivity patterns at these frequencies as in previous literature in disorders of consciousness patients.[20]

Conflicts of interest

None.

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Data availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2019.05.021.

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