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EEG functional connectivity contributes to outcome prediction of postanoxic coma

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HIGHLIGHTS

- Early EEG recordings under 48 h after cardiac arrest allow for prediction of outcome of coma patients.
- EEG-based functional connectivity features hold potential to improve outcome prediction of comatose patients after cardiac arrest.
- The most accurate prediction model combined functional connectivity and non-coupling EEG metrics, showing the best results to date.

ABSTRACT

Objective: To investigate the additional value of EEG functional connectivity features, in addition to non-coupling EEG features, for outcome prediction of comatose patients after cardiac arrest.
Methods: Prospective, multicenter cohort study. Coherence, phase locking value, and mutual information were calculated in 19-channel EEGs at 12 h, 24 h and 48 h after cardiac arrest. Three sets of machine learning classification models were trained and validated with functional connectivity, EEG non-coupling features, and a combination of these. Neurological outcome was assessed at six months and categorized as "good" (Cerebral Performance Category [CPC] 1–2) or "poor" (CPC 3–5).
Results: We included 594 patients (46% good outcome). A sensitivity of 51% (95% CI: 34–56%) at 100% specificity in predicting poor outcome was achieved by the best functional connectivity-based classifier at 12 h after cardiac arrest, while the best non-coupling-based model reached a sensitivity of 32% (0–54%) at 100% specificity using data at 12 h and 48 h. Combination of both sets of features achieved a sensitivity of 73% (50–77%) at 100% specificity.
Conclusion: Functional connectivity measures improve EEG based prediction models for poor outcome of postanoxic coma.
Significance: Functional connectivity features derived from early EEG hold potential to improve outcome prediction of coma after cardiac arrest.

1. Introduction

Early prediction of neurological outcome in postanoxic coma patients remains a challenge. With bilateral absence of somatosensory evoked potentials or bilateral absence of pupillary light and corneal reflexes, 10–20% of patients with poor outcome can be detected reliably (Sandroni et al. 2014; Rossetti et al. 2016). EEG approaches have shown to be of relevant additional value, reaching

Abbreviations: EEG, electroencephalography; ICU, intensive care unit; CPC, cerebral performance category; SSEP, somatosensory evoked potential; COH, coherence; ciCOH, corrected imaginary coherence; PLV, phase locking value; ciPLV, corrected imaginary phase locking value; MI, mutual information; BT, bagged tree; LSVM, linear support vector machine; CI, confidence interval, ROC, receiving operating characteristic; AUC, area under the curve.

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50–66% sensitivity for reliable prediction of poor or good outcome (Tjepkema-Cloostermans et al. 2015, 2019; Rossetti et al. 2016; Ruijter et al. 2019). Generalized suppression (<10 μV) and synchronous patterns with $\geq$ 50% suppression at 12–24 h after cardiac arrest are invariably associated with a poor outcome. Otherwise, evolution towards a continuous EEG pattern within 12 h after cardiac arrest is strongly associated with a good outcome (Sivaraju et al. 2015; Spalletti et al. 2016; Ruijter et al. 2019). However, prognosis of many patients remains uncertain, which leads to a prolonged and possibly futile treatment in intensive care units (ICUs).

Most EEG research in this field entails visual interpretation. This requires extensive training, is time-consuming, and suffers from inter-rater variability. Computer assisted approaches allow for objective interpretation and may outperform visual assessment. Proposed computer assisted methods for prediction of postanoxic coma poor outcome include features from the frequency, amplitude, and entropy domains with random forest classification (Tjepkema-Cloostermans et al. 2017; Nagaraj et al. 2018), regression analysis modeling (Ruijter et al. 2018), and deep learning (Tjepkema-Cloostermans et al. 2019). Herewith, reliable prediction of a poor outcome was possible in up to 62–66% of patients.

Functional connectivity, defined as the statistical interdependence of two EEG time-series based on their phase, amplitude or spectrum, has been associated with good or poor outcome after cardiac arrest (Beudel et al. 2014; Zubler et al. 2016, 2017), showing potential for outcome prediction. Functional connectivity analysis is based on the assumption that synchronization of activity between distant brain regions underlies physiological neuronal communication and integration (Fries 2015). Since cardiac arrest leads to a cascade from synaptic failure towards neuronal cell death (Hofmeijer and van Putten 2012; Norton et al. 2012), we expect functional connectivity to be altered in these patients.

In this work, we investigate the value of numerous and complementary functional connectivity features in postanoxic coma to predict neurological outcome in a large multicenter cohort of comatose patients after cardiac arrest. Additionally, we study their evolution over time, which has, to the best of our knowledge, never been done before. Finally, we study the additional predictive value of functional connectivity features to state-of-the-art prognostication using quantitative non-coupling EEG features. Previous electrophysiology studies focused in postanoxic coma patients or subjects with consciousness disorders have found that a decreased connectivity or power in the alpha band and an increase in these parameters in the delta band is associated with poor outcome (Nenadovic et al. 2014; Hong and Su 2017; Şerban et al. 2017; Chatelle et al. 2018). Therefore, we hypothesize that similar changes in connectivity in these bands will be observed, and that the parameters obtained from these frequency bands will have a higher relevance in the prediction of outcome of postanoxic coma patients.

2. Materials and methods

2.1. Design and patients

We performed a post hoc analysis of a prospective cohort study on EEG-based outcome prediction of patients suffering from coma after cardiac arrest. Consecutive comatose (Glasgow Coma Scale score $\leq$ 8) patients after cardiac arrest were prospectively included from June 2010 to December 2017 at the Medisch Spectrum Twente and Rijnstate hospital, two Dutch teaching hospitals. Exclusion criteria included severe traumatic brain injury, acute stroke, previous dependency in daily living (Cerebral Performance Category [CPC] 3 or 4), and progressive neurodegenerative disease. This dataset has been partially used in preceding articles focused on outcome prediction after cardiac arrest using visual assessment (Cloostermans et al. 2012; Hofmeijer et al. 2015; Tjepkema-Cloostermans et al. 2015; Sondag et al. 2017; Glimmerveen et al. 2019; Ruijter et al. 2019) or quantitative analysis (Tjepkema-Cloostermans et al. 2013, 2017; Ruijter et al. 2018). The Medical Research Ethics Committee Twente dismissed the need for informed consent for EEG monitoring during the ICU stay and clinical follow-up, since EEG monitoring is part of the usual routine care in both hospitals. Data were anonymized before further processing.

Neurological functional outcome, expressed as the score on the five-point Glasgow-Pittsburgh cerebral performance category (CPC) (Jennett and Bond 1975), was used as the primary outcome measure, and dichotomized as good (CPC 1–2, none/moderate neurological deficits with autonomy in daily life) or poor (CPC 3–5, severe disability/vegetative state/death). Outcome was registered by one of three investigators during a standardized telephone interview with the patient or patient's legal representative at six months after hospitalization (BR, MTC, HK). CPC scores were estimated using a Dutch translation of the EuroQol-6D questionnaire (Hoeymans et al. 2005).

2.2. Treatment and EEG recordings

Postanoxic comatose patients were treated in accordance with standard protocols at the hospitals. Temperature of 33 or 36 °C was induced after arrival on the ICU and maintained for 24 h; for more details, see (Hofmeijer et al. 2015). In short, fentanyl or remifentanil and propofol were used for sedation and analgesia at the Medisch Spectrum Twente. At the Rijnstate hospital, patients were provided a combination of midazolam, propofol and morphine. Continuous EEG recordings were started between 8 AM and 8 PM after admission to the ICU, and always within 24 h after cardiac arrest. Twenty-one silver/silver chloride electrodes were positioned according to the international 10–20 system on the scalp. EEG recordings were performed with a sampling frequency of 256 Hz with a Neurocenter EEG (Medisch Spectrum Twente) or 500 Hz with a Nihon Kohden system (Rijnstate). EEG was extracted until patients recovered consciousness or until it was decided to withdraw treatment. However, EEG recordings were always stopped after 5 days in the ICU.

2.3. Withdrawal of treatment

Withdrawal of life-sustaining treatment was contemplated only after 72 hours since the return of spontaneous circulation, when the patient was off sedation and back to normothermia. The final decision was based on international guidelines, which included bilateral absence of short latency somatosensory evoked potentials (SSEPs), incomplete return of brainstem reflexes, and absent or extensor motor responses (Sandroni et al. 2014; Rossetti et al. 2016). Sporadically, decisions on treatment withdrawal were taken between 48 and 72 hours when absent SSEP responses were observed. While EEG data within 72 h were not used for decisions regarding treatment withdraw, physicians were not blinded to the EEG, as they had to assess the treatment of electrographic seizures.

2.4. EEG preprocessing

Analysis of the EEG data was performed offline and using MATLAB (MATLAB Release R2018B The Math-Works, Inc.). Some of the scripts developed used functions from FieldTrip (Oostenveld et al. 2011), and GLMNET (Qian et al. 2013). Firstly, all the data was filtered and downsampled to 256 Hz, if necessary. Afterwards, an automated custom computer algorithm was used (Tjepkema-Cloostermans et al. 2013), automatically extracting 5-

minute artifact-free EEG segments for each hour up to 120 hours after cardiac arrest. Before any subsequent analysis, the EEG was re-referenced to a 19-channel longitudinal bipolar montage.

Visual EEG assessment has shown the highest predictive values between 12 and 48 hours after resuscitation (Hofmeijer and van Putten 2016). Therefore, 5-minute EEG epochs at 12, 24 and 48 hours were used. In the case that no epoch was available at these time points, e.g. because of artifacts, the closest artifact-free epoch in the range of ± 2 h was used. These epochs were band-pass filtered with a FIR window filter (1024th order, built using a Chebyshev window) into Delta (1–4 Hz), Theta (4–8 Hz), Alpha (8–12 Hz), Beta1 (12–18 Hz), Beta2 (18–25 Hz), and Gamma (25–45 Hz) frequency bands. Connectivity features used in this study were calculated separately for each frequency band.

2.5. Connectivity features extraction

We estimated three complementary connectivity features: coherence (COH, (Enochson and Otnes 1965)), Phase Locking Value (PLV, (Lachaux et al. 1999; Aydore et al. 2013)) and mutual information (MI, (Cellucci et al. 2005)). COH and PLV are sensitive to volume conduction, meaning that spurious zero-lag connectivity could potentially affect them. To prevent influence of volume conduction, corrected imaginary COH (ciCOH, (Ewald et al. 2012)) and corrected imaginary PLV (ciPLV, (Bruña et al. 2018)), insensitive to the contribution of zero-lag synchronization, were also included.

The 5-minute EEG epochs were subdivided in segments of 10 seconds each. The first and the last segments were discarded to correct for the border effect of the filtering process. The connectivity features were calculated in each of the remaining segments, then averaged over all segments. As COH gives a value per frequency step, the band-wise COH value was calculated as the average of the value in each frequency step within the band limits.

2.6. Feature matrix construction

The calculation of each connectivity feature yields a matrix of dimensions 19x19 for each 5-minute epoch and frequency band, depicting the functional connectivity between any pair of electrodes. The high number of connectivity features calculated requires a dimensionality reduction, for which the average of the whole connectivity matrix excluding the diagonal and the average connectivity per channel were calculated. Three basic graph theory features from the weighted functional networks were obtained from the connectivity matrices: Clustering Coefficient (Onnela et al. 2005), Characteristic Path Length (Antoniou and Tsompa 2008), and Efficiency (Latora and Marchiori 2001).

PLV, ciPLV, and mutual information can be calculated independently in each 10-second segment, and thus the mean and the variance of the graph features and the variance of the average connectivity were calculated as well, adding seven more features per frequency band and connectivity feature in those cases. Therefore, the final feature vector for each subject had dimension n = 816 (Table 1).

Furthermore, given the importance of the evolution of EEG within 48 hours after return of spontaneous circulation (Hofmeijer et al. 2015; Ruijter et al. 2018), the creation of groups containing all possible combinations of sets of features extracted at 12, 24 and 48 hours was considered pertinent in this study. Thus, patients were subdivided regarding the availability of recordings at these different time stamps.

2.7. Outcome prediction

Machine learning techniques were used to combine all features in a model to predict outcome. The creation of classifiers followed the diagram shown in Fig. 1, which stands as a classical procedure for the creation of a machine learning classifier. The subjects were randomly allocated to two groups (Figure 1, D1): the training set, which is used to train and adjust the parameters of the classifiers (80% of subjects), and a test set, with which the predictive power of the trained classification models is evaluated (remaining 20% of subjects).

The classifiers were created using the individual datasets extracted at different timestamps as well as all their possible combinations (which we will call temporal subsets), resulting in 7 different sets of classifiers (12 h, 24 h, 48 h, 12&24 h, 12&48 h, 24&48 h, 12&24&48 h). The combined datasets only included data from patients with EEG epochs available in all the included time points.

From all available features, a selection of features is made using an elastic net algorithm (Zou and Hastie 2005), implemented in MATLAB. An equal weight was given to both L1 and L2 penalties on which this algorithm is based (α = 0.5), being consequently designed to deal with possible collinearities between features and remove redundancies among variables while keeping all the relevant information. The program ran over the same dataset 500 times, and every feature that was selected at least once by the elastic net algorithm was used in the classification model training (Figure 1, D2).

The model was trained to predict poor outcome with 100% specificity. For the training we used a 5-fold cross-validation. Two types of machine learning classifier models were used: bagged trees (BT), which is a Random Forest classifier with an additional bootstrapping step added in order to avoid biased results, and linear support vector machine (LSVM), which defines a linear hyperplane separator to assign new events to the different possible categories. Initially non-probabilistic, the LSVM can be transformed to probabilistic classifiers thanks to the Platt scaling method (Platt et al., 1999). The whole procedure was repeated over 500 times to obtain the 95% confidence interval (CI) for the classification task.

2.8. Additional value of functional connectivity

To assess the additional value of functional connectivity features to non-coupling EEG features, we created two additional classifiers sets. The first was trained with 44 non-coupling EEG features as used in (Nagaraj et al. 2018), which are based in the amplitude evolution, frequency distribution, and entropy (the amount of statistical information a random variable presents) of EEG time-series. The second set of classifiers was trained with both functional connectivity and non-coupling features.

2.9. Statistics

Between-groups comparisons were assessed with a Mann-Whitney U test for continuous data, a Fisher's Exact test for categorical data, and a binomial test for dichotomous data. *p*-values < 0.05 were considered statistically significant. All results for classification performance are stated as median (95% CI) unless stated otherwise.

Discriminative values of prediction models of the test and training sets were assessed as sensitivity at 100% specificity and AUC of Receiver Operator Characteristic (ROC, including 95% confidence interval (CI)) analyses. Also, predictive values for prediction of outcome were calculated using Receiver Operator Characteristic (ROC) of the training and test sets. For prediction of poor outcome, predictive values were expressed as sensitivity (95%CI) at a specificity level of 100% in the training set, and as sensitivity (95%CI) and specificity (95%CI) in the test set. Since models were trained for optimal prediction of poor outcome, the predictive features for

Table 1
Functional connectivity features calculated for every 5-minute EEG epoch in this study. COH: coherence; ciCOH: corrected imaginary coherence; PLV: phase locking value; ciPLV: corrected imaginary phase locking valiue; MI: mutual information. "Total" means that the feature was calculated from the averaged connectivity matrix, while mean & variance indicates that the features were calculated from the connectivity matrices at each 10 second segment, before their averaging.

Connectivity measure	Feature	Total	Mean & Variance	Number of features	Total number of features
COH	Total average connectivity	√	X	1	23
	Average connectivity per channel	√	X	19	
	Clustering coefficient	√	X	1	
	Characteristic Path Length	√	X	1	
	Efficiency	√	X	1	
ciCOH	Total average connectivity	√	X	1	23
	Average connectivity per channel	√	X	19	
	Clustering coefficient	√	X	1	
	Characteristic Path Length	√	X	1	
	Efficiency	√	X	1	
PLV	Total average connectivity	√	√	2	30
	Average connectivity per channel	√	X	19	
	Clustering coefficient	√	√	3	
	Characteristic Path Length	√	√	3	
	Efficiency	√	√	3	
ciPLV	Total average connectivity	√	√	2	30
	Average connectivity per channel	√	X	19	
	Clustering coefficient	√	√	3	
	Characteristic Path Length	√	√	3	
	Efficiency	√	√	3	
MI	Total average connectivity	√	√	2	30
	Average connectivity per channel	√	X	19	
	Clustering coefficient	√	√	3	
	Characteristic Path Length	√	√	3	
	Efficiency	√	√	3	
				Number of frequency bands	x 6
				Final number of features	816

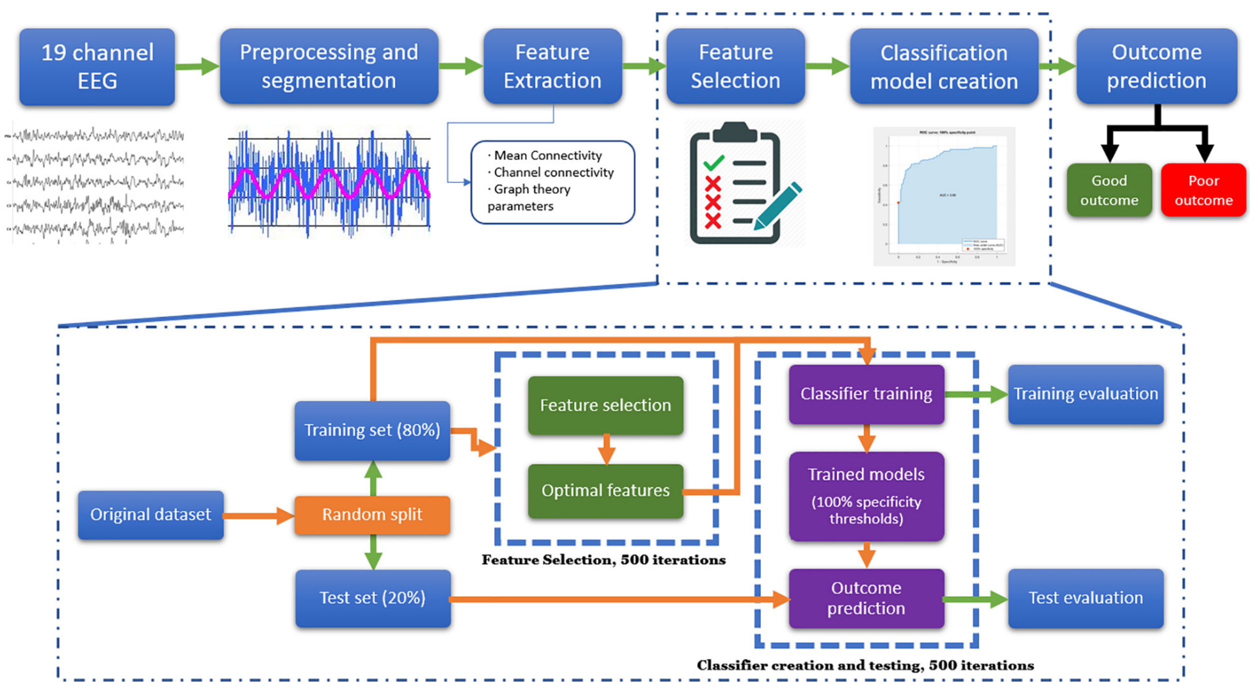

Fig. 1. Flowchart showing the complete process the data undergo in this analysis, as well as the procedure to create the classifiers. This includes acquisition of the data (A), cleaning and preprocessing of the data (B), the calculation of the connectivity features (C), feature selection with an elastic net algorithm (D), training of the classifiers for a 100% specificity classification (E1), selection of the best classifiers (E2), and performance evaluation of the classifiers at the test set (F).

good outcome were only reported for the test set. Predictive values for good outcome were expressed as sensitivity (95%CI) at a specificity level of 95% in the test set only. Note that the meaning of sensitivity and specificity depend on the classification objective. If the focus is prediction of poor outcome, sensitivity refers to the percentage of poor outcome subjects correctly classified, and specificity to the percentage of good outcome subjects correctly assessed. If the focus is prediction of good outcome, the definitions are switched.

With the objective of interpreting our results, and observe the direction of the changes in connectivity, a post-hoc statistical test comparing average connectivity was performed only if any feature was selected by the feature selection algorithm in all the best classifiers in at least 80% of the iterations (400 out of 500 iterations).

All statistical analyses were performed using MATLAB.

3. Results

3.1. Demographic information

Data from 594 patients were included, of whom 46% had a good outcome. Table 2 contains their baseline characteristics, as well as data about the sedatives used in their treatment. Supplementary Materials Tables 1 and 2 include the demographics per hospital.

3.2. Performance in the training set

The number subjects included, number of features remaining after the feature selection process, and sensitivities of the trained classifiers at different temporal subsets, are shown in Table 3. Most subsets required 31–46 features to be implemented in the classifier. The classifiers using subsets of patients at 12 h, 12 h&48 h and 12 h&24 h&48 h achieved the highest predictive values in the training set (sensitivity 34–73% at 100% specificity) and were further validated in the test set. Supplementary Materials Tables 3, 4, and 5 show which specific features were used for the training of these classifiers.

Table 2
Summary of baseline characteristics of patients included in this study. Maximum rates of sedative medication refer to the maximum doses within the first 24 h after cardiac arrest. OHCA: Out-of-hospital CA; VF: Ventricular fibrillation; VT: Ventricular tachycardia.

	Good outcome (n = 294)	*Poor outcome (n = 300)*	*p-value*
Male (%)	227 (77)	224 (74)	0.5
Age (mean ± SD)	59 ± 12	65 ± 13	<0.001
OHCA (%)	270 (92)	264 (90)	0.14
Primary cardiac cause (%)	262 (89)	210 (70)	<0.001
Shockable First rhythm (VF/VT) (%)	273 (93)	174 (58)	<0.001
Treated with propofol in First 24hr (%)	253 (86)	253 (84)	0.06
Max propofol rate (mg/kg/h)	2,9 ± 1,2	2,7 ± 1,1	0.01
Treated with midazolam in First 24hr (%)	89 (30)	98 (33)	0.44
Max midazolam rate (µg/kg/h)	118,0 ± 73,0	134,8 ± 95,7	0.2
Treated with fentanyl in First 24hr (%)	129 (44)	152 (51)	0.22
Max fentanyl rate (µg/kg/h)	1,2 ± 0,7	1,6 ± 0,7	0.009
Treated with remifentanil in first 24hr (%)	17 (6)	25 (4)	0.28
Max remifentanil rate (µg/kg/h)	7,8 ± 4,5	4,7 ± 3,4	0.016
Treated with morphine in first 24hr (%)	111 (38)	97 (32)	0.14
Max morphine rate (µg/kg/h)	25,9 ± 11,4	28,7 ± 11,2	0.08

3.3. Performance in the test set

The functional connectivity-based classifier that achieved the highest sensitivity and specificity for prediction of poor outcome in the test set was the LSVM classifier at 12 hours after cardiac arrest (sensitivity = 51% (34–56) and specificity = 100% (100–100); Fig. 2 Green). Performance of all classifiers in the test set is shown in Table 4.

The best performance for prediction of good outcome was observed in the same classifier (sensitivity = 69% (69–69) and specificity = 95%; Fig. 3).

3.4. Additional value of functional connectivity

The best performance obtained by the non-coupling EEG features classifiers in the test set was achieved by the BT classifier

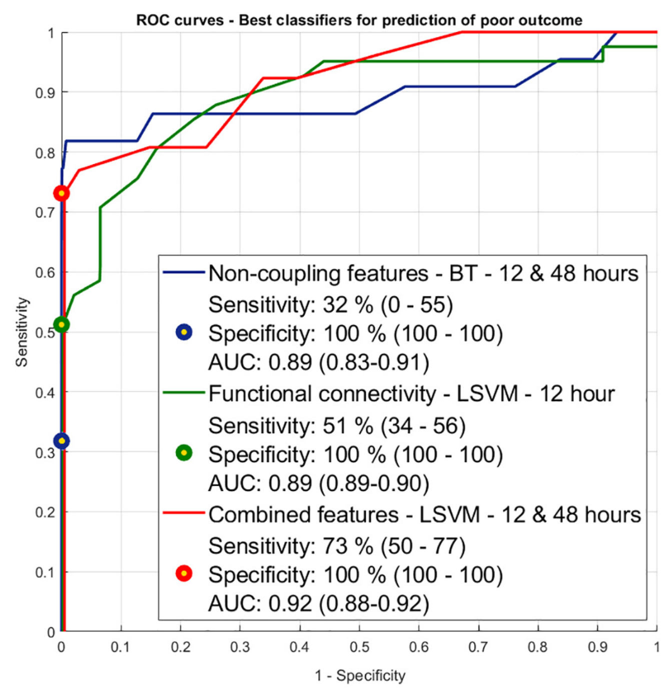

Fig. 2. ROC curve for prediction of poor outcome in the test set trained only with non-coupling features (blue), only with functional connectivity features (green), and both groups of features (red). The circular markers of the same colors correspond to the actual classification performance of the respective classifiers. ROC: Receiver Operating Curve, LSVM: Linear Support Vector Machine, BT: Bagged Trees. All classification parameters are expressed as median (95% Confidence Intervals).

Table 3
Number of features included in the functional connectivity classifier training after the feature selection process and performance of the classifiers in the training set for prediction of poor outcome. The bold lines indicate the temporal subsets that were selected as best in the training phase. BT: Bagged Trees; LSVM: Linear Support Vector Machine. Sensitivity at 100% specificity is depicted in percentage (%) and expressed as median (95% Confidence Interval).

Subset	*Patients*	*Good outcome*	*Poor outcome*	*Features for classifier training*	*LSVM Sensitivity100*	*BT Sensitivity100*
12 h	**366**	**185**	**181**	**40**	**40 (31–51)**	**34 (11–49)**
24 h	537	279	258	31	26 (18–33)	11 (3–24)
48 h	405	197	208	112	12 (7–20)	11 (3–25)
12 h & 24 h	333	177	156	39	24 (16–43)	21 (2–40)
12 h & 48 h	**238**	**126**	**112**	**46**	**73 (56–80)**	**67 (48–76)**
24 h & 48 h	375	187	188	34	15 (10–22)	23 (9–36)
12 h & 24 h & 48 h	**232**	**123**	**109**	**41**	**46 (32–60)**	**61 (38–74)**

Table 4
Performance of the functional connectivity classifiers in the test set for prediction of poor outcome. BT: Bagged Trees; LSVM: Linear Support Vector Machine. Sensitivity and specificity are depicted in percentage (%) and are expressed as median (95% Confidence Intervals).

Subset	*LSVM*		*BT*	
	Sensitivity	*Specificity*	*Sensitivity*	*Specificity*
12 h	51 (34–56)	100 (100–100)	37 (15–51)	100 (100–100)
12 h & 48 h	41 (27–50)	96 (96–96)	32 (18–41)	96 (96–100)
12 h & 24 h & 48 h	29 (24–52)	92 (92–96)	43 (24–62)	92 (92–96)

at the 12&48 hours temporal subset (sensitivity = 32% (0–55) and specificity = 100% (100–100); Fig. 2 Blue). The best performance achieved by the classifiers trained with both non-coupling features and functional connectivity features was attributed to the LSVM classifier at the 12 & 48 hours subset (sensitivity = 73% (50–77) and specificity = 100% (100–100); Fig. 2 Red). Area under the curve (AUC) of models based on functional connectivity features, non-coupling EEG features, and a combination of both sets of features were 0.89 (0.89–0.90), 0.89 (0.83–0.91), and 0.92 (0.92–0.92), respectively. Fig. 4 displays the ROC curves in the training and the test set of the best classifiers for each set of features used in this study.

3.5. Post-hoc connectivity analysis

Only 5 features were selected in all the best classifiers at least in 80% of the iterations of the feature selection algorithm: PLV theta Cz, PLV theta T3, PLV alpha Fp2, ciCOH Beta Cz, PLV Delta F3. The statistical tests comparing average connectivity in these parameters and frequency bands are shown in Fig. 5. Delta PLV connectivity shows significantly higher values in poor outcome patients after 24 hours from cardiac arrest. On the other hand, alpha and theta PLV connectivity have significantly higher values in good outcome patients at 12 hours and 24 hours after cardiac arrest. Nevertheless, this difference becomes insignificant at 48 hours after cardiac arrest. Finally, Beta2 ciCOH is always significantly higher in poor outcome patients.

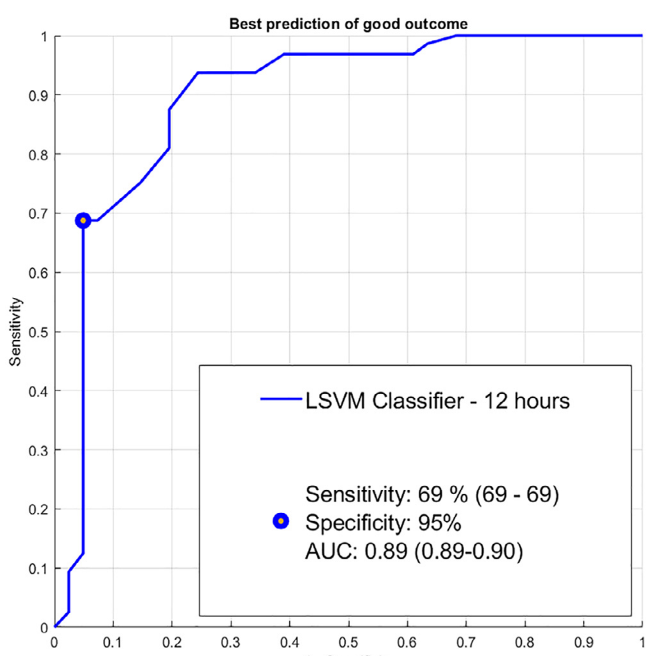

Fig. 3. ROC curve for the best prediction of good outcome in the test set, with the LSVM classifier at the 12 hour temporal subset. Sensitivity at 95% specificity is marked in the figure, and classification parameters are expressed as median (95% Confidence Intervals). ROC: Receiver Operating Curve, LSVM: Linear Support Vector Machine.

4. Discussion

We show that the use of EEG-based functional connectivity features can significantly improve reliable early prediction of poor outcome in comatose patients after cardiac arrest. We evaluated their predictive ability using machine learning algorithms, both for the functional connectivity measures alone and in combination with non-coupling EEG metrics. In both cases the results outperform current approaches in medical practice (Sandroni et al. 2014; Rossetti et al. 2016). The combination of coupling and non-coupling features achieves significantly higher predictive values than any other method in literature until now (Tjepkema-Cloostermans et al. 2013, 2017, 2019; Hofmeijer et al. 2015; Zubler et al. 2016, 2017; Sondag et al. 2017; Nagaraj et al. 2018; Ruijter et al. 2018, 2019). Given that prognostication of postanoxic coma patients still remains a challenge, the development of a methodology for a reliable outcome prediction in these patients is of high necessity. The classifier presented in this study stands as a great improvement in sensitivity and specificity when compared to any previous methodology, allowing for avoidance of futile treatment, minimizing erroneous classification of patients that would survive, and helping in the patient's relatives emotionally compromised situation.

All functional connectivity features in this study were calculated offline, making this technique less suitable to implement in today's clinical practice. However, their calculation and testing take only a few minutes in a conventional laptop, and EEG devices are rapidly evolving and will soon be able to calculate these parameters in real time. Regarding this aspect, it is also important to remark the simplicity of the 19-electrode EEG setting used in this project.

4.1. Functional connectivity as outcome predictor

Using functional connectivity features alone for prediction of poor outcome, we obtained a better sensitivity than approaches currently used in clinical practice (Sandroni et al. 2014; Rossetti et al. 2016), such as the bilateral absence of N20, while maintaining a 100% specificity. Performance equals that of other quantitative EEG approaches that have been proposed (Zubler et al. 2016, 2017; Tjepkema-Cloostermans et al. 2017; Nagaraj et al. 2018). Amongst these, one used functional connectivity (Zubler et al. 2017), which reported an AUC of 0.81, a sensitivity of 54% (27–83) by selecting the 100% specificity point at the test ROC curve, using a dataset of 94 patients. As compared to this previous report, our classifiers using only functional connectivity features for prediction of poor outcome achieved a higher AUC (0.89 (0.89–0.90)), and a similar sensitivity (51% (36–56)) at specificity of 100% (100–100). These improvements may have resulted from the larger number of features and using sensitivity at 100% specificity for the optimization of the classifiers at the training phase. The larger cohort resulted in smaller confidence intervals. To

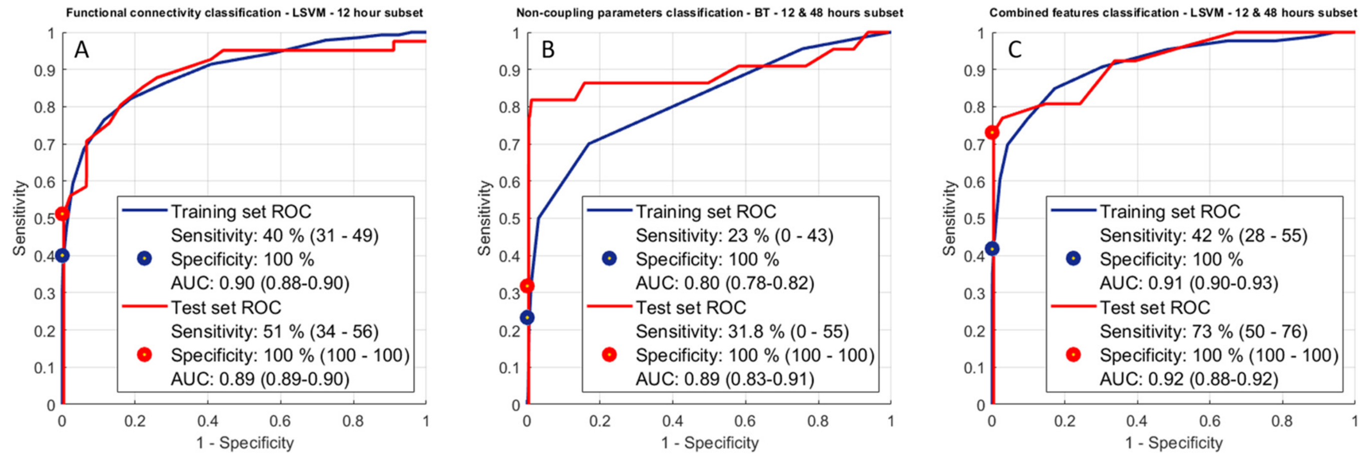

Fig. 4. ROC curves for prediction of poor outcome from the best classifiers at the training (blue) and the test set (red) for each subset of features (A: functional connectivity; B: non-coupling features; C: combination of both feature groups). The markers highlighted along the curves represent the performance of the classifiers. ROC: Receiver Operating Curve, LSVM: Linear Support Vector Machine, BT: Bagged Trees. All classification parameters are expressed as median (95% Confidence Intervals).

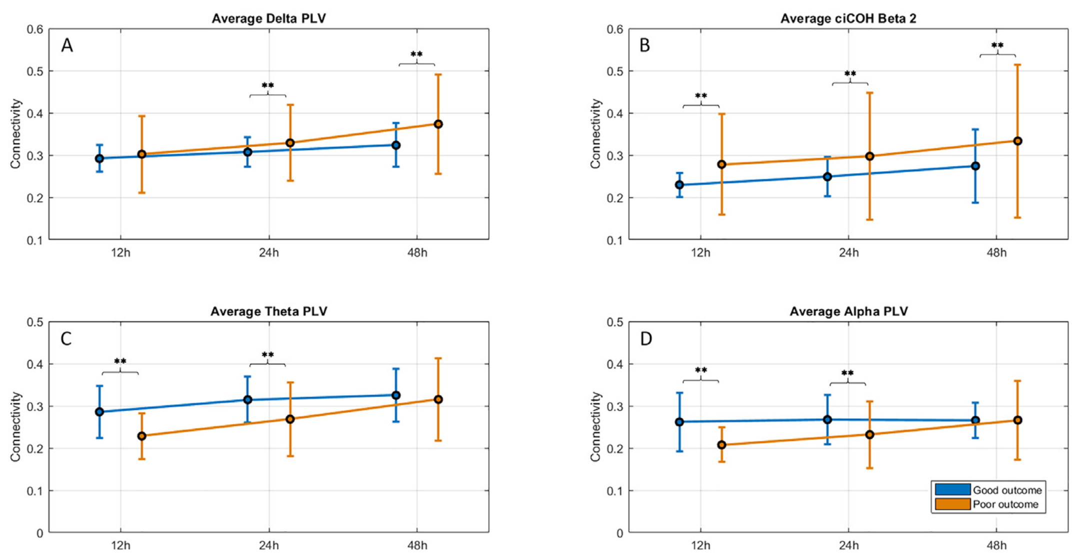

Fig. 5. Differences in delta, beta2, theta and alpha connectivity between good outcome (blue) and poor outcome (orange) patients. A: average PLV connectivity over all electrodes in the delta frequency band over time. B: average ciCOH connectivity over all electrodes in the beta2 frequency band over time. C: average PLV connectivity over all electrodes in the theta frequency band over time. D: average PLV connectivity over all electrodes in the alpha frequency band over time. * corresponds to p-values < 0.05; ** corresponds to p-values < 0.05 * 10^{-5}. PLV: Phase Locking Value; ciCOH: corrected imaginary coherence.

obtain a comparison with visual inspection, we compared our results with those of (Ruijter et al. 2019), which give a recent insight on the performance of visual inspection analysis. The best performance for prediction of poor outcome in this study was achieved inspecting data at 12 hours after cardiac arrest, showing a sensitivity of 47% (42–51 95%CI) and a specificity of 100% (100–100 95%CI), which are similar results to those obtained with our classifiers trained only with functional connectivity. Regarding prediction of good outcome, functional connectivity achieves a higher sensitivity (69% (69–69)) at 95% specificity (95% (95–95)) than previous work in the field, which reported sensitivities of approximately 50% at 90% specificity (Tjepkema-Cloostermans et al. 2013, 2017; Sondag et al. 2017; Ruijter et al. 2018, 2019).

However, it is the addition of functional connectivity features to non-coupling EEG features that brings out the most important finding in this study. The combination of both sets of features showed a better performance in predicting poor outcome than using each set individually, and, to the best of our knowledge, a better performance than any other prognostication methodology for postanoxic coma proposed until now, both based on visual inspection and quantitative analysis (Cloostermans et al. 2012; Tjepkema-Cloostermans et al. 2013, 2015, 2017, 2019; Hofmeijer et al. 2015; Zubler et al. 2016, 2017; Sondag et al. 2017; Nagaraj et al. 2018; Ruijter et al. 2018, 2019). However, it is difficult to fairly compare all these approaches because of the different datasets used in each of them, and the different methodology for classification and validation strategy. The improvement in classification obtained with our new model may have resulted from the combination of the high sensitivity at 100% specificity in the training set ($Se_{100} = 80\%$, Fig. 4B) from the non-coupling EEG features, and the high generalizability of the functional connectivity models, observed from the similarity of both its training and test ROC curves (Fig. 4A).

The highest predictive values were achieved using data from both 12 and 48 hours after cardiac arrest, showing that this approach can be used for early detection of poor outcome patients. In accordance with previous reports, most of the prognostic information in the EEG seems to be found as early as 12 hours after the cardiac arrest (Hofmeijer et al. 2015; Tjepkema-Cloostermans et al. 2017; Ruijter et al. 2019). However, most classifiers benefitted from the addition of the recordings 48 hours after this episode. One possible explanation for this is that, after 12 hours, good outcome patients might already start showing a transition towards a continuous EEG state. This might be especially true for functional connectivity, as it could indicate a normalization of the communication between different cortical areas. Using a similar logic, the recordings 48 hours after cardiac arrest would procure information about those patients less likely to recover, probably because they still show a brain pattern in the range of brain damage and did not migrate towards normalization yet. The data collected at 24 hours after cardiac arrest could represent a grey area in which the evolution of both good outcome and poor outcome patients is still not clear. This emphasizes the need for a long-term monitoring of patients' brain activity, as the information after 12 and after 48 seems complementary for a correct prognosis.

The feature selection process revealed a higher predictive power from PLV parameters, which were twice more likely to be selected as relevant, and a lower contribution of COH features to the classifiers, which were selected less than 10% the times than PLV metrics. The rest of the connectivity features calculated were selected approximately half the times compared to PLV parameters. It is important to remark that PLV features were mostly extracted from delta, theta and alpha frequency bands and from the 12 h subset. Our conclusion is that a multi-parameter approach as the one performed in this study helped the classifiers achieve a higher accuracy, as we could assess both linear and nonlinear connectivity, and both zero-lag connectivity and lagged connectivity. While the connectivity measures included in this study are chosen based on their widespread use in previous studies, and because of their complementarity to each other, many other measures are however available, meaning that future studies can investigate on the additional performance in outcome prediction these can provide.

Additionally, the feature selection process showed 5 parameters that were included in at least 80% of the iterations throughout all the best classifiers: PLV theta Cz, PLV theta T3, PLV alpha Fp2, ciCOH Beta Cz, PLV Delta F3. In our case, these parameters refer to the average connectivity of those specific channels with the rest of the EEG electrodes. The post-hoc analysis revealed an increased functional connectivity in the delta and beta2 bands, which is in accordance with literature. Previous studies report an association between poor outcome and increased power or connectivity in these bands, both in postanoxic comatose patients and subjects showing minimally conscious or vegetative state (Nenadovic et al. 2014; Şerban et al. 2017; Chatelle et al. 2018). On the other hand, connectivity in the theta and alpha bands had a different behaviour. At 12 hours after cardiac arrest, good outcome patients presented a higher PLV than poor outcome patients (Fig. 5C and 5D). However, the difference in theta and alpha PLV connectivity is progressively lost in subsequent temporal datasets (Fig. 5C and 5D, from p-values $< 0.05 * 10^{-5}$ at 12 and 24 hours after cardiac arrest, to p-values of 0.23 and 0.94 for theta and alpha connectivity at 48 hours after cardiac arrest respectively). The pathophysiology of this evolution is not well understood yet, but initial suppression of excitatory and inhibitory synaptic activity with a subsequent variable long-term potentiation is a potential mechanism that has been proposed in (Ruijter et al. 2017). Future studies should thrive to clarify the role of these frequency bands in postanoxic coma.

4.2. Strengths and limitations

Our work was based on a large prospectively collected cohort, implying a high data quality and ascertainment. The complementarity of the calculated features allowed for the creation of classifiers that have avoided overfitting, thus presenting a high performance in the prediction task at hand.

On the other hand, the study has some limitations. Firstly, we did not incorporate any local features in our analyses, since postanoxic encephalopathy affects the whole brain. Moreover, our EEG setup has a relatively low spatial resolution and individual-electrode based metrics are sensitive to noise and artifacts. Given that the setup of these EEG caps requires special skills, it would also be interesting to test the prognostic value of the metrics presented in this study when acquired through technologies that are more user-friendly and wearable, such as dry-electrode EEG systems. Secondly, although we used cross validation and split the data in training and test set, there is no truly external validation set. The performance of the classifiers trained with functional connectivity features combined from different time points showed a reduction in both sensitivity and specificity when evaluated in the test set. At the same time, the BT classifiers generally did not show a sensitivity as high as that of the LSVM classifiers. Overfitting might be the reason behind these results, favored by the higher number of features included in the classification models in the first case, and by the higher complexity of the BT classifier in the second. Lastly, a potential problem in unblinded studies investigating diagnostic accuracy is the self-fulfilling prophecy (Geocadin et al. 2012). This characterizes almost all studies on this topic. EEG classifications were assigned offline, blinded for patients' outcome, but attending physicians were not blinded to the EEG registration. However, it is important to state that guidelines on treatment withdrawal were strictly followed, and these do not include any aspects from the EEG during the first 72 hours.

5. Conclusion

We demonstrate that EEG functional connectivity features are reliable predictors of poor neurological outcome and add to EEG based poor outcome prediction after cardiac arrest. The combination of functional connectivity features and EEG non-coupling features led to higher predictive values than any previously reported model for prediction of poor outcome (sensitivity = 73% (50–76), specificity = 100% (100–100) and AUC = 0.92 (0.92–0.92)).

Declaration of Competing Interest

M.J.A.M. van Putten is co-founder of Clinical Science Systems, a supplier of EEG systems for Medisch Spectrum Twente. The other authors declare that they have no competing interests.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2021.02.011.

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