Dynamic functional connectivity of the EEG in relation to outcome of postanoxic coma

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Abstract
Objective: Early EEG contains reliable information for outcome prediction of comatose patients after cardiac arrest. We introduce dynamic functional connectivity measures and estimate additional predictive values.

Methods: We performed a prospective multicenter cohort study on continuous EEG for outcome prediction of comatose patients after cardiac arrest. We calculated Link Rates (LR) and Link Durations (LD) in the α, β, and θ band, based on similarity of instantaneous frequencies in five-minute EEG epochs, hourly, during 3 days after cardiac arrest. We studied associations of LR and LD with good (Cerebral Performance Category (CPC) 1–2) or poor outcome (CPC 3–5) with univariate analyses. With random forest classification, we established EEG-based predictive models. We used receiver operating characteristics to estimate additional values of dynamic connectivity measures for outcome prediction.

Results: Of 683 patients, 369 (54%) had poor outcome. Patients with poor outcome had significantly lower LR and longer LD, with largest differences 12 h after cardiac arrest (LRa 1.87 vs. 1.95 Hz and LDa 91 vs. 82 ms). Adding these measures to a model with classical EEG features increased sensitivity for reliable prediction of poor outcome from 34% to 38% at 12 h after cardiac arrest.

Conclusion: Poor outcome is associated with lower dynamics of connectivity after cardiac arrest.

Significance: Dynamic functional connectivity analysis may improve EEG based outcome prediction.

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1. Introduction

Approximately half of all comatose patients after cardiac arrest die or have lasting, severe impairments resulting from permanent brain damage (Nielsen et al., 2013, Ruijter et al., 2018). Early information about the likelihood of good or poor neurological recovery contributes to decisions on continuation of life sustaining treatment. With a combination of neurological examination, somatosensory evoked potentials (SSEP) and electroencephalogra-
ph (EEG), reliable prediction of good or poor recovery is possible in approximately 50% of patients within three days after cardiac arrest (Glimmerveen et al., 2019, Hofmeijer et al., 2015, Rossetti et al., 2016, Ruijter et al., 2018, Ruijter et al., 2019, Sandroni et al., 2014a).

Qualitative or quantitative analyses of continuous EEG have the largest added value for outcome prediction if measured within the first 24 hours after cardiac arrest (Hofmeijer et al., 2015, Jonas et al., 2019, Ruijter et al., 2018, Spalletti et al., 2016, Tjepkema-Cloostermans et al., 2019, Tjepkema-Cloostermans et al., 2017). The EEG signal reflects synaptic activity, which is one of the first neuronal functions that is interrupted by anoxia or ischemia (Hofmeijer et al., 2014). This is reflected by suppressed EEG patterns in almost all comatose patients directly after cardiac arrest. Synaptic failure may be reversible within minutes to hours, with recovery of physiological EEG rhythms. Restoration of continuous EEG background activity within 12 hours after resuscitation reflects reversible synaptic failure and is a strong indicator of a good neurological recovery (Hofmeijer et al., 2019, Sivaraju et al., 2015, Spalletti et al., 2016). Otherwise, persistent suppression of the EEG background pattern (<10 μV), with or without pathologic synchronous activity, is invariably associated with poor outcome (Hofmeijer et al., 2015, Ruijter et al., 2019).

The predictive value of EEG for outcome prediction after cardiac arrest may be approved by adding an estimate of functional connectivity to the classical EEG measures. Functional connectivity is a measure of statistical interdependency between brain regions and is assumed to reflect functional interactions between these regions. Postanoxic encephalopathy causes disturbances in neuronal networks, that may be reflected by alterations in functional connectivity.

Functional connectivity is of increasing interest in many fields of EEG research. Among others, functional connectivity measures have been proposed for diagnosis or prediction of delirium (Numan et al., 2017), epilepsy (van Diessen et al., 2013), or Alzheimer's disease (Miraglia et al., 2017). Few studies have investigated connectivity in association with neurological recovery after cardiac arrest (Beudel et al., 2014, Cimpaneriu et al., 2002, Maybhate et al., 2013, Nenadovic et al., 2014, Zubler et al., 2016, Zubler et al., 2017). These have shown desynchronization of the EEG within the first hour after cardiac arrest (Cimpaneriu et al., 2002, Maybhate et al., 2013). Various connectivity measures, such as higher clustering coefficients, lower average path length, and a higher small world index, have been identified as possible predictors of poor neurological recovery (Beudel et al., 2014, Zubler et al., 2016, Zubler et al., 2017). Predictive values were independent of anesthetic drugs and treatment with therapeutic hypothermia.

Most studies regard interactions between neuronal networks as static, presenting a single measure of connectivity per patient (van Diessen et al., 2015). This is biologically unlikely (Friston, 2000, Rudrauf et al., 2006), since neural assemblies are known to dynamically interact (Varela et al., 2001). Also, none of the previous studies provided an estimation of the additional value of connectivity measures, in addition to other quantitative EEG measures. In this study, we propose a dynamic functional connectivity approach. We assess the value of dynamic functional connectivity measures to discriminate between comatose patients after cardiac arrest with good and poor outcome. Also, we study the additional value to other quantitative EEG features, for prediction of outcome.

2. Methods

2.1. Study design

We performed a prospective cohort study on consecutive, adult, comatose patients after cardiac arrest (Glasgow Coma Scale score < 8), admitted to the ICU of two teaching hospitals in the Netherlands (Medisch Spectrum Twente (MST) and Rijnsmeer hospital) between June 2010 and June 2018. Exclusion criteria were concomitant acute stroke, traumatic brain injury, hanging/choking, auto-intoxication, anaphylactic shock, drowning, pre-existing dependency in daily living, severe spinal cord injury, or progressive neurodegenerative disease. EEG data for this analysis were collected on the Intensive Care Units (ICUs). The need for informed consent for EEG measurements on the ICU and follow-up by telephone interview was waived, since EEG monitoring is part of standard care in the participating hospitals. Data of the first 681 patients, included up to November 2017 has been used in earlier publications (Hofmeijer et al., 2015, Ruijter et al., 2019).

2.2. Treatment

‘Patients were treated according to national and local protocols. This included targeted temperature management at 33 °C or 36 °C, starting immediately after arrival at the ICU department and maintained for at least 24 hrs. In the Rijnstate hospital, propofol, midazolam and morphine were the preferred sedative and analgesic drugs. In the Medisch Spectrum Twente, patients received mainly propofol and either fentanyl or remifentanil. Mostly, analgesosedation was discontinued at a body temperature of 36.5 °C. In both hospitals, a non-depolarizing muscle relaxant (rocuronium or atracurium) was occasionally added in case of severe compensatory shivering.’ (Hofmeijer et al., 2015)

2.3. Decisions on withdrawal of treatment

Withdrawal of treatment was considered > 72 h after cardiac arrest, during normothermia, and off sedation. Decisions on treatment withdrawal were based on international guidelines (Nolan et al., 2015, Sandroni et al., 2014a). In short, WLST was considered in a multidisciplinary meeting, when at least one of the following was present:

- Wide pupils, unresponsive to light > 48 h after cardiac arrest, off sedation
- Absent N20 response of the SSEP, >48 h after cardiac arrest, during normothermia and off sedation

When the clinical state of the patient did not improve > 3–7 days after cardiac arrest, with persistent absent or extensor motor responses, incomplete return of brainstem reflexes, or treatment resistant myoclonus, WLST could be considered, depending on the patients’ previous wishes, co-morbidity, and other organ failure. Decision-making on WLST was always centred around the individual patient at stake and in close consultation with the patients’ family. In case of doubt, we observed and re-evaluated.

Discontinuation of life sustaining treatment was sporadically initiated between 48 h and 72 h in case of absent SSEP responses. EEG data were not used for decisions regarding treatment withdrawal (Hofmeijer et al., 2015)

2.4. EEG measurements

‘Continuous EEG monitoring was started as soon as possible after arrival at the ICU, but for practical reasons always between 8AM and 8PM. Twenty-one silver/silver chloride electrodes were placed on the scalp according to the international 10–20 system. A Neurocenter EEG recording system (Clinical Science Systems, Leiden, The Netherlands) or a Nihon Kohden system (VCM Medical, Leusden, The Netherlands) were used for the recordings. Intensive care physicians were blinded, but consulting neurologists were not
2.5. Outcome

The primary outcome measure was neurological outcome expressed as the score on the five-point Glasgow-Pittsburgh Cerebral Performance Category (CPC) at six months (Cummins et al., 1991). Outcome was dichotomized as “good” (CPC 1–2) or “poor” (CPC 3–5), as recommended by the International Liaison Committee on Resuscitation (Perkins et al., 2015).

CPC scores were obtained by telephone follow-up at 6 months by one of the investigators, blinded for EEG patterns and SSEP recordings. Scoring was based on a Dutch translation of the EuroQol-6D questionnaire. CPC scores were also collected at three months. We used outcome at 3 months for patients who were alive but for whom the 6 months was not available.

2.6. EEG preprocessing

Of the EEG recordings in the first 72 hours after cardiac arrest, 5 minutes epochs were automatically selected, one for every consecutive hour after cardiac arrest (Tjepkema-Cloostermans et al., 2013). Data were referenced to the average montage. A previously described automated artefact rejection algorithm was applied to remove channels containing artefacts (Ruijter et al., 2018). This algorithm checks for muscle artefacts, non-physiological high amplitudes and flat channels. When an epoch contained less than 15 artefact free channels, the epoch was considered unreliable and discarded from further analyses.

Epochs that passed the artefact rejection algorithm were further processed. Epochs were recorded at a sampling rate of 500 Hz or 250 Hz, and resampled to 250 Hz when necessary. Thereafter, the signals were filtered according to three common frequency bands (delta, 1–4 Hz; theta, 4–8 Hz and alpha, 8–13 Hz), using a zero-phase fourth order Butterworth bandpass filter. EEG analysis was performed off-line.

2.7. Connectivity

We applied a dynamic approach of network analysis, acknowledging the temporal dynamics of interactions between brain networks, by calculating link rates and link durations (van Putten, 2003) based on frequency synchronization.

Phase synchronization is a well-known measure of functional connectivity between a pair of neuronal assemblies, and is independent from the amplitude of the signal (Varela et al., 2001). Phase synchronization occurs if the phases \( \phi \) of two signals \( i \) and \( j \) synchronize over time \( t \), expressed as

\[
\Delta \phi(t) = \phi_i(t) - \phi_j(t) = \text{constant.} \tag{1}
\]

The phase locking condition is defined between pairs of signals and assumes time stability of the phase differences (Rudrauf et al., 2006). For a given pair of signals, \( \phi_i(t) \) and \( \phi_j(t) \), the notion of frequency synchrony is the derivative of the phase difference in Eq. (1). Hence

\[
\frac{1}{2\pi} \left[ \frac{d\Delta \phi_i(t)}{dt} - \frac{d\Delta \phi_j(t)}{dt} \right] = v_i(t) - v_j(t) \approx 0 \tag{2}
\]

with \( v_i(t) \) the instantaneous frequency of oscillator \( i \). Therefore, conservation of a phase difference during a period of time implies that both oscillators possess the same instantaneous frequency during this period. Using the condition expressed in Eq. (2), it is possible to track phase synchrony over multiple frequencies, including non-stationary time frequency couplings (Rudrauf et al., 2006).

EEGs generally contain multiple superimposed rhythms, as well as noise. We first apply the short time Fourier transform (STFT), to obtain a time–frequency representation (TFR) of the signal. We use a window of 450 samples (1.8 s) with 449 samples overlap. Then we use the Ridge algorithm to extract the frequencies from the local maxima of this time–frequency representation. These are the TFR peaks, or ridges, of the EEG, and are an estimation of the instantaneous frequency (Iatsenko et al., 2016, Rudrauf et al., 2006).

These ridges can be mapped in a binary matrix in the time frequency plane, called the ridge curve (Fig. 1). When ridge curves of two signals are superimposed, pairwise correlation between two oscillators is present when their ridge curves overlap (Fig. 1). At these moments, we assume a functional link between the brain regions generating the EEG signal. We assume that functional connectivity between channel pairs \( i \) and \( j \) exists if it holds that their ridge curves, i.e. their TFR peaks, overlap, for at least a duration of 4 samples. This is evaluated for all possible electrode combinations and for the whole epoch.

From these pairwise correlation maps we calculated link rates (LR) for each pair of electrodes \( i \) and \( j \), defined as the number of connections (links) \( N \) between the two channels in the period \( \Delta t \) using

\[
LR_{ij} = \frac{N_{ij}}{\Delta t} \tag{3}
\]

We define link durations (LD) according to (van Putten, 2003):

\[
LD_{ij} = \frac{\sum_{k=1}^{m} t_k}{N_{ij}} \tag{4}
\]

with \( t_k \) the mean duration of an individual link \( k \), and \( N \) the number of links between electrodes \( i \) and \( j \).

For each patient, the average LR and LD of the whole brain were calculated per epoch for each of the three frequency bands. LR and LD represent the number of links per second and the mean duration of these links, averaged over all channel combinations. We therefore refer to LR and LD as measures of functional connectivity dynamics.

2.8. Random forest classifiers

To estimate the value of LR and LD in addition to classical quantitative EEG (qEEG) parameters for discrimination between...
patients with good and poor outcome and prediction of neurological recovery after cardiac arrest, we established a model containing a combination of qEEG features that contributed to reliable outcome prediction according to previous analyses (Tjepkema-Cloostermans et al., 2017). From 5-minute EEG epochs at 12 and 24 hours after cardiac arrest, we extracted the qEEG features: Alpha-Delta Ratio, signal power, Shannon Entropy, delta coherence, regularity, and a differentiation measure between regular burst suppression and burst suppression with identical bursts. Clinical parameters, such as age and sex, where not included in the current model, since these parameters do not improve model performance (Tjepkema-Cloostermans et al., 2017). Two random forest classifiers, based on 500 individual decision trees, were fitted to the qEEG results at 12 and 24 hours after cardiac arrest respectively. The maximum number of terminal nodes was set to 5. Subsequently, two additional random forest classifiers were created, based on the original qEEG features and LR and LD at 12 and 24 hours after cardiac arrest. link rates and link durations were added and model performances were compared as described under 2.9. Models were created using a random forest classifier based on 500 individual decision trees at 12 and 24 hours after cardiac arrest. Random forest classification was done using the software package R (version 2015; R Foundation for Statistical Computing, Vienna, Austria) and the randomForest package (Liaw and Wiener, 2002).

2.9. Statistical analysis

Patient characteristics are presented in a descriptive way and compared with Fisher’s exact test for categorical variables and the Mann-Whitney U-test for continuous variables.

The LRs and LDs of the good and poor outcome groups are graphically presented as the median and interquartile range (IQR) for every hour after cardiac arrest in each frequency band. Group differences of LR and LD between patients with good and poor outcome were analyzed using the Mann-Whitney U-test at 12, 24, 36, 48, 60 and 72 hours after cardiac arrest. We considered a p-value < 0.05 as statistically significant.

Discriminative values of the 4 random forest classifiers were assessed as the area under the curve (AUC) of Receiver Operator Characteristic (ROC, including 95% confidence interval (CI)) analyses. Also, predictive values for prediction of outcome were derived from the ROC curve. For poor outcome prediction, predictive values are expressed as sensitivity (95%CI) at a specificity level of 100%. Predictive values for good outcome are expressed as sensitivity at a specificity level of 80%. McNemar tests are used to compare predictive values for prediction of poor outcome.

All analyses, except the random forest classifiers, were performed using MATLAB (MATLAB Release R2018b, The MathWorks, Inc.).

3. Results

We included 709 patients. Of these, 26 were lost to follow-up and were excluded from further analysis. This resulted in 683 remaining patients for the current analysis. Of 17 patients, outcome at 3 months was used, because outcome at 6 months was unavailable. Three hundred and sixty nine patients (54%) had a poor neurological outcome. Baseline characteristics are presented in Table 1. Supplementary Table A.1 lists the number of in- and excluded epochs at the most important time points since cardiac arrest.

### Table 1

Baseline characteristics of the study population. Patients with poor neurological outcome are generally older and more often have a non-cardiac cause of the arrest than patients with good outcome.

|                          | Good outcome (n = 314) | Poor outcome (n = 369) | P-value |
|--------------------------|------------------------|------------------------|---------|
| Female (%)               | 70 (22%)               | 93 (25%)               | 0.42    |
| Age (years)              | 60 ± 12                | 65 ± 13                | <0.001* |
| Shockable rhythm (%)     | 284 (91%)              | 207 (56%)              | <0.001* |
| Number of OHCA           | 290 (92%)              | 328 (78%)              | 0.19    |
| Presumed cause of CA     |                        |                        |         |
| Cardiac                  | 281 (90%)              | 253 (69%)              | <0.001* |
| Non-cardiac              | 16 (5%)                | 76 (21%)               | <0.001* |
| Unknown                  | 17 (5%)                | 40 (11%)               | <0.05   |

P-values marked with * indicate a statistically significant difference between patients with good and poor outcome.

OHCA: Out of Hospital Cardiac arrest, CA: cardiac arrest.

3.1. Link rates

In the delta band, LR was significantly lower for patients with poor outcome than for patients with good outcome at 12 and 24 hours after cardiac arrest (p < 0.01), and significantly higher at 48, 60 and 70 hours after cardiac arrest (p < 0.01, p < 0.01 and p = 0.01 respectively) (see Fig. 2A). In the theta band, LR was significantly lower in the poor outcome group at 12, 24, and 36 hours after cardiac arrest (p = 0.01, p < 0.01 and p < 0.01 respectively) (see Fig. 2B). In the alpha band, no differences were seen in LR between patients with good and poor outcome (see Fig. 2C). The IQR of the LR in patients with poor outcome is broader than for the patients with good outcome. Median values and group differences for LR in the various frequency bands are given in Supplementary Table A.2. EEG fragments of subjects with relative high or low LR values are pro

A discrete group effect might be present, but LR did not allow for prognostication for single patients (Fig. 2D). LR predicts poor outcome at 100% specificity with a sensitivity of 1% (95%CI 0–5%) in the delta band, of 8% (95%CI 5–13%) in the theta band, and 3% (95%CI 1–7%) in the alpha band. Predictive values for prediction of poor and good outcome at all time points after cardiac arrest can be found in Supplementary Table A.2.

3.2. Link durations

In the delta band, LD is significantly higher for patients with poor outcome than for patients with good outcome in the first 36 hours (p < 0.01) (see Fig. 3A). In the theta band, LD is higher in patients with poor outcome at all time (p < 0.01), with the largest difference in the first 12 hours (see Fig. 3B). LD in the alpha band is also higher for patients with poor outcome at all time (p < 0.01 at 12, 24, 36 and 58 hours, p = 0.03 at 60 hours and p = 0.02 at 72 hours), with the largest difference in the first 12 hours (see Fig. 3C). IQR of the LD in patients with poor outcome is broader than for patients with good outcome. Median values and group differences for LD in the various frequency bands are given in Supplementary Table A.3.

Despite a clear difference in median LD is seen at 12 hours after cardiac arrest, predictive values are low (Fig. 3D). At 100% specificity, LD predicts poor outcome with a sensitivity of 7% (95%CI 4–12%) in the delta band, of 7% (95%CI 3–12%) in the theta band and a sensitivity of 11% (95%CI 6–16%) in the alpha band. Predictive values for prediction of poor and good outcome at all time points after cardiac arrest can be found in Supplementary Table A.3.

Typical examples of EEG patterns that can be seen after cardiac arrest, with corresponding LR and LD values are presented in Fig. 4.
3.3. Additional value

Discriminative values of random forest classifiers at 12 and 24 hours after cardiac arrest containing only qEEG features and of classifiers based on qEEG and LR and LD are essentially equal (Fig. 5). By adding LR and LD to the classifiers, reliable prediction of poor outcome slightly improves, with a sensitivity at 100% specificity from 34% (95%CI: 25–42%) to 38% (95%CI: 30–46%) at 12 h after cardiac arrest (p = 0.35), and from 15% (95%CI: 11–20%) to 22% (95%CI: 17–28%) at 24 hour after cardiac arrest (p = 0.01).

4. Discussion

With this study we introduce an EEG-based dynamic measure of functional connectivity, acknowledging that functional interactions between brain regions are dynamic rather than static. We demonstrate that comatose patients with good and poor neurological outcome after cardiac arrest show different dynamics of brain functional connectivity. Differences in LR and LD between patients with good and poor outcome are most prominent in the first 36 hours after cardiac arrest, with lower LR and higher LD in patients with poor outcome than for patients with good outcome. Early after resuscitation, patients with good neurological outcome show a higher frequency of dynamic interactions than patients with poor outcome, presumably reflecting more functional connections. This suggests that more severe postanoxic encephalopathy is associated with less dynamic interactions between brain regions.

Despite statistically significant differences on a group level, LR and LD have limited predictive values as single predictors of outcome. When added to a prediction model of other quantitative EEG parameters, sensitivity for prediction of poor outcome at 100% specificity slightly increases at 12 hr, and significantly increases at 24 hr after cardiac arrest. This may indicate that dynamic connectivity measures hold potential to contribute to outcome prediction after cardiac arrest. However, discrimination on a group level, defined as AUC, remains practically the same.

Failure of synaptic transmission as a result of ATP depletion is one of the earliest consequences of cerebral anoxia (Bolay et al., 2002, Hofmeijer et al., 2014, Hofmeijer and van Putten, 2012). This failure of transmission reduces the capability of synchrony binding between neuronal assemblies. After severe anoxia, synaptic failure may become irreversible, and structural deficits will add to failure of functional connectivity (Beudel et al., 2014, Hofmeijer et al., 2014). In small scale networks, oscillatory synchronization of distant groups of neurons has been shown to correlate with functional activity of the brain (Stopfer et al., 1997). Although LR and LD are able to measure synchrony binding between distant brain regions, we can only speculate about their biological substrate within these large scale neurological networks.

Our results are in line with those of Nenadovic and colleagues, who investigated the variability of phase synchrony as a predictor of cerebral recovery after coma in children aged 0–17 years old. They found that patients with poor neurological recovery showed lower temporal variability of connectivity than patients with favorable outcome, in the absence of visually manifest improvement of the EEG (Nenadovic et al., 2014). Our results are also in line with previous studies on static functional connectivity measures, showing associations between altered connectivity and poorer outcome (Beudel et al., 2014, Cimponeriu et al., 2002, Maybhate et al., 2013, Nenadovic et al., 2014, Zubler et al., 2016, Zubler et al., 2017).
The large IQR of dynamic connectivity measures in patients with a poor outcome likely reflects the large variation of EEG patterns seen in patients with a poor outcome. The EEG fragments shown in Fig. 4 illustrate this. As for many quantitative EEG measures, it remains unclear whether LR and LD are providing new, relevant information. Synchronous burst suppression patterns and generalized periodic discharges, result from pathological synchronization probably resulting in increased connectivity (van Putten, 2003, Zubler et al., 2017). On the other hand, physiological synchronization is hampered in patients with burst suppression, low voltage and isoelectric EEG patterns. The variations in EEG background activity and dynamic connectivity measures are compelling and invite further analysis.

4.1. Study limitations and future perspectives

The connectivity approach used in this study is based on links between pairs of signals and did not consider the possibility of multiple brain regions connecting at the same time. As a result, links may have been found between areas, that are actually orchestrated by a third brain area (Bastos and Schoffelen, 2015). The currently proposed method can be adapted to study synchronization between groups of signals, by combining multiple EEG traces in one IFH map. This could be useful to apply in further research on LR and LD. Also, the spatial distribution of LR and LD over the scalp could add to discriminatory or predictive values. Since some brain areas are more sensitive to cerebral hypoxia than other, alterations in LR and LD could differ between brain areas. However, EEG is most sensitive to activity of the cerebral cortex, but will provide less insight in the functioning of other structures, such as the deep grey nuclei.

Our method suffers from volume conduction, indicating that EEG time series recorded from nearby electrodes will also record activity from shared neural sources, which gives rise to spurious correlations between these time series (Bastos and Schoffelen, 2015). Correction for volume conduction can be achieved by excluding “connections” with a constant phase difference of 0 or a modulus of π. Herewith, only non-zero phase locking will be taken into account, which can never be a result of volume conduction (Bastos and Schoffelen, 2015, Stam et al., 2007).

As in every study on outcome prediction after cardiac arrest, we cannot fully exclude self-fulfilling prophecy. Although the EEG was not incorporated in decisions regarding WLST, treating physicians were not blinded to the recordings. Results on dynamic connectivity where not available at the time of decision making. We did not incorporate clinical measures, such as age, duration of resuscitation and presence of brain stem reflexes in our classifier. This was decided because these measures did not improve model performance in a previous model based on qEEG parameters (Tjepkema-Cloostermans et al., 2017). However, after further optimization and validation of this method, the established classifier could possibly be of clinical use in addition to clinical measures.

Since dynamic connectivity has never been investigated before in this population, we performed an exploratory study. We intended to get an impression of the usability of these measures, and did not correct for multiple comparisons. This may have resulted in an overestimation of the results. Further validation of these measures should incorporate correction for multiple measures, for example using Bonferroni’s method.
Fig. 4. Examples of four EEG fragments of comatose patients, 24 hours after cardiac arrest. 4A: patient with good outcome, showing a continuous EEG pattern with LR\(_h\) 2.24 Hz and LD\(_h\) 83 ms. 4B, 4C and 4D: EEG traces of patients with poor outcome, 4B: a low voltage pattern LR\(_h\) 1.46 Hz and LD\(_h\) 336 ms, 4C: synchronized burst suppression pattern, LR\(_h\) 1.10 Hz and LD\(_h\) 76 ms, and 4D: generalized periodic discharges, LR\(_h\) 2.64 Hz and LD\(_h\) 124 ms. The wide ranges of LR and LD in patients with poor outcome are obviously associated with visually manifest variations in EEG patterns. LR = Link Rates; LD = Link Durations.

Fig. 5. Receiver operating characteristics of EEG based random forest classifiers for prediction of poor outcome at 12 (A) and 24 (B) hours after cardiac arrest. The first classifier (light blue) is based on the original quantitative EEG (qEEG) features (Alpha-Delta Ratio, signal power, Shannon Entropy, delta coherence, regularity, and a differentiation measure between regular burst suppression and burst suppression with identical bursts). The second classifier (dark blue) is based on the original qEEG features, combined with dynamic connectivity (DC) measures: Link Rate and Link Duration. Adding dynamic connectivity measures to the original qEEG measures did not improve discrimination between patients with good and poor outcome (expressed as area under the curve (AUC)), but slightly improved predictive values for reliable prediction of poor outcome.
For this study, data analyses were performed off line, using a high end computer. The computations are demanding an take considerable time, up to 15 minutes per 5 minute EEG epoch. This high computational demand makes the method currently less suitable for implementation at the bedside.

5. Conclusion

LR and LD are EEG measures of functional connectivity dynamics. Patients with good neurological outcome show more dynamic interactions between brain regions early after resuscitation than patients with poor outcome. Dynamic functional connectivity analysis may hold potential to add to EEG based outcome prediction of comatose patients after cardiac arrest, and merit further research.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2020.10.024.

References

Bastos AM, Schoffelen JM. A Tutorial Review of Functional Connectivity Analysis Methods and Their Interpretational Pitfalls. Front Syst Neurosci 2015;9:175. Beudel M, Tjepkema-Cloostermans MC, Boersma JH, van Putten MJ. Small-world characteristics of EEG patterns in post-anoxic encephalopathy. Front Neuro 2014;5:97. Bolay H, Gursoy-Ozdiren Y, Sara Y, Onur R, Can A, Dalkara T. Persistent Defect in Transmitter Release and Synapsin Phosphorylation in Cerebral Cortex After Transient Ischemic Injury. Stroke 2002;33(5):1369–75. Cimponeriu L, Tong S, Bezerianos A, Thakor NV. Synchronization and information processing across the cerebral cortex following cardiac arrest injury. Houston, TX, USA: IEEE; 2002. Cummins RO, Chamberlain DA, Abramson NS, Allen M, Basket PJ, Becker L, et al. Recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest: The Utstein Style. A statement for health professionals from a task force of the American Heart Association, the European Resuscitation Council, the Heart and Stroke Foundation of Canada, and the Australian Resuscitation Council. Circulation 1991;84(2):960–75. Friston KJ. The labile brain. I. Neuronal transients and nonlinear coupling. Philos Trans R Soc Lond B Biol Sci 2000;355(1394):215–36. Glimmerveen AB, Ruijter BJ, Keijzer HM, Tjepkema-Cloostermans MC, van Putten M, Hofmeijer J. Association between somatosensory evoked potentials and EEG in comatose patients after cardiac arrest. Clin Neurophysiol 2019;130 (11):2026–31. Hofmeijer J, Beerink TMJ, Bosch FH, Beishuizen A, Tjepkema-Cloostermans MC, van Putten MJAM. Early EEG contributes to multimodal outcome prediction of postanoxic coma. Neurology 2015;85(2):137–43. Hofmeijer J, Mulder AT, Farinha AC, van Putten MJ, le Feber J. Mild hypoxia affects synaptic connectivity in cultured neuronal networks. Brain Res 2014;1557:180–9. Hofmeijer J, van Putten MJ. Ischemic cerebral damage: an appraisal of synaptic failure. Stroke 2012;43(2):607–15. Iatsenko D, McClintock PVE, Stefanovska A. Extraction of instantaneous frequencies from ridges in time–frequency representations of signals. Signal Process 2016;125:290–303. Jonas S, Rossetti AO, Oddo M, Jenni S, Favaro P, Zubler F. EEG-based outcome prediction after cardiac arrest with convolutional neural networks: Performance and visualization of discriminative features. Hum Brain Mapp 2019. Liaw A, Wiener M. Classification and regression by random forest. R News 2002;2 (18):22. Maybath A, Chen C, Abkari Y, Sherman DL, Shen K, Jia X, et al. Band Specific Changes in Thalamocortical Synchrony in Field Potentials after Cardiac Arrest Induced Global Hypoxia. Osaka, Japan: IEEE; 2013. Miraglia F, Vecchio F, Rossini PM. Searching for signs of aging and dementia in EEG through network analysis. Behav Brain Res 2017;317:292–300.

Nenadovic V, Perez Velazquez JL, Hutchison JS. Phase synchronization in electroencephalographic recordings prognosticates outcome in paediatric coma. PLoS ONE 2014;9(4):e94942. Nielsen N, Weterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, et al. Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest. N Engl J Med 2013;369(23):2197–206. Nolan JP, Soar J, Carcassi A, Cronberg T, Moulard VR, Deakin CD, et al. European Resuscitation Council and European Society of Intensive Care Medicine Guidelines for Post-resuscitation Care 2015: Section 5 of the European Resuscitation Council Guidelines for Resuscitation 2015. Resuscitation 2015;95:202–22. Numan T, Slooter AJC, van der Kooi AW, Hoekman AML, Suyker WJL, Stacj CM, et al. Functional connectivity and network analysis during hypoxic delirium and recovery from anesthesia. Clin Neurophysiol 2017;128(6):914–24. Perkins GD, Jacobs IG, Nadkarni VM, Berg RA, Bhanji F, Bierent D, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update of the Utstein Resuscitation Registry Templates for Out-of-Hospital Cardiac Arrest: a statement for healthcare professionals from a task force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian and New Zealand Council on Resuscitation, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa, Resuscitation Council of Asia); and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. Circulation 2015;132(13):1286–300. Rossetto AO, Rabinstein AA, Oddo M. Neurological prognostication of outcome in patients in coma after cardiac arrest. Lancet Neurol 2016;15(6):597–600. Rudrauf D, Douiri A, Kovach C, Lachaux JP, Cositi D, Mathieu C, et al. Frequency flows and the time-frequency dynamics of multivariate phase synchronization in brain signals. Neuroimage 2006;31(1):209–21. Ruijter BJ, Hofmeijer J, Tjepkema-Cloostermans MC, van Putten M. The prognostic value of discontinuous EEG patterns in postanoxic coma. Clin Neurophysiol 2018;129(8):1534–43. Ruijter BJ, Tjepkema-Cloostermans MC, Tromp SC, van den Bergh WM, Foudaine NA, Komrij FHM, et al. Early electroencephalography for outcome prediction of postanoxic coma: A prospective cohort study. Ann Neuro 2019;86(2):203–14. Sandroni C, Cariou A, Cavallaro F, Cronberg T, Friberg H, Hoedemaekers C, et al. Prognostication in comatose survivors of cardiac arrest: an advisory statement from the European Resuscitation Council and the European Society of Intensive Care Medicine. Intensive Care Med 2014a;40(12):1816–31. Sivaraju A, Gilmore EJ, Wira CR, Stevens A, Rampal N, Moeller JL, et al. Prognostication of post-cardiac arrest coma: early clinical and electroencephalographic predictors of outcome. Intensive Care Med 2015;41(12):764–72. Spalletti M, Carrai R, Scarpino M, Cossu I, Ammannati A, Ciapetti M, et al. Single electroencephalographic patterns as specific and time-dependent indicators of good and poor outcome after cardiac arrest. Clin Neurophysiol 2016;127(7):2610–7. Stacj CM, Nolte G, Daffertshofer A. Phase lag index: assessment of functional connectivity from multi channel EEG and MEG with diminished bias from common sources. Hum Brain Mapp 2007;28(11):1787–93. Stopfer M, Bhagavan S, Smith BH, Laurent G. Impaired odour discrimination on desynchronization of odour-encoding neural assemblies. Nature 1997;390(6657):90–4. Tjepkema-Cloostermans MC, da Silva LC, Ruijter BJ, Tromp SC, Drost G, Komrij FHM, et al. Outcome Prediction in Postanoxic Coma With Deep Learning. Crit Care Med 2019. Tjepkema-Cloostermans MC, Hofmeijer J, Beishuizen A, Hom HW, Blans MJ, Bosch FH, et al. Cerebral Recovery Index: Reliable Help for Prediction of Neurologic Outcome After Cardiac Arrest. Crit Care Med 2017;45(8):e789–97. Tjepkema-Cloostermans MC, van Meulen FB, Meinsma G, van Putten MJAM. A Cerebral Recovery Index (CRI) for early prognosis in patients after cardiac arrest. Crit Care 2013;17(5):R252. van Dieessen E, Diederens SJ, Braun KP, Jansen FE, Stacj CM. Functional and structural brain networks in epilepsy: what have we learned?. Epilepsia 2013;54(11):1855–65. van Dieessen E, Numan T, van Dellen E, van der Kooi AW, Boersma M, Hofman D, et al. Opportunities and methodological challenges in EEG and MEG resting state functional brain network research. Clin Neurophysiol 2015;126(8):1468–81. van Putten MJ, Propose linked results in the human brain. J Neurosci Methods 2003;127(1):1–10. Varela F, Lachaux JP, Rodriguez E, Martinerie J. The brainweb: Phase synchronization and large-scale integration. Nat Rev Neurosci 2001;2:229–39. Zubler F, Koening C, Steimer A, Jakob SM, Schindler KA, Gast H. Prognostic and diagnostic value of EEG signal coupling measures in coma. Clin Neurophysiol 2016;127(7):2942–52. Zubler F, Steimer A, Kurmann R, Bandarabadi M, Noy J, Gast H, et al. EEG synchronization measures are early outcome predictors in comatose patients after cardiac arrest. Clin Neurophysiol 2017;128(4):635–42.

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