Correlation of quantitative EEG and cognitive impairment in cardiac arrest survivors: first steps towards a prediction model

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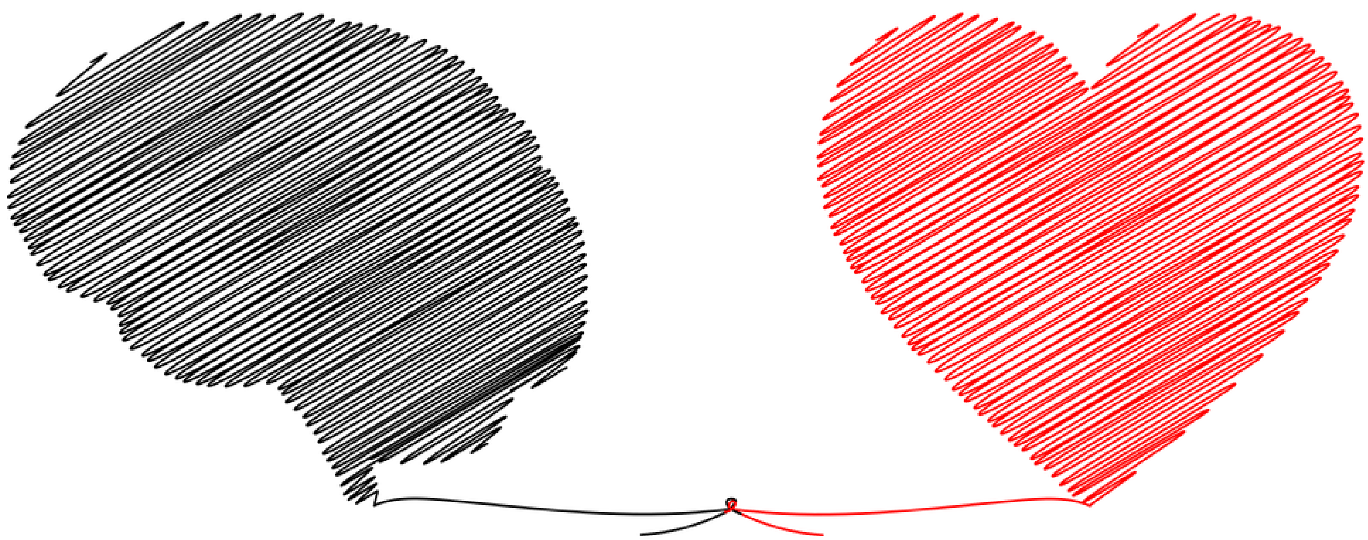

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Abstract

Background: Half of the cardiac arrest survivors experience long-term cognitive impairment. Cognitive rehabilitation might have beneficial effects on cardiac arrest survivors. Therefore, early identification of patients at risk for developing long-term cognitive impairment is important. To date, early predictors for long-term cognitive functioning are not available yet. Here we study the potential role of early EEG.

Objectives: Primary objective is to study the association between quantitative EEG (qEEG) measures and cognitive functioning in cardiac arrest survivors. Secondary objective is to examine the predictive value of early qEEG measures in addition to demographic and clinical parameters for predicting cognitive impairment during hospital admission.

Methods: We performed a prospective longitudinal cohort study on cardiac arrest survivors in six Dutch hospitals. Resting-state nineteen-channel EEG was recorded during hospital admission. We selected eyes closed segments to calculate alpha-to-theta ratio, peak frequency, center of gravity, and global and local imaginary coherency. The primary outcome measure was Montreal Cognitive Assessment (MoCA) obtained during hospital admission. We assessed the correlations between the MoCA and qEEG measures with Pearson's correlation coefficient. We performed multinomial logistic regression analyses to examine the added predictive value of qEEG measures for prediction of cognitive impairment (MoCA<26). Five-fold validation was used for model validation.

Results: We included 77 cardiac arrest survivors, of whom 53 had cognitive impairment. We found a positive significant correlation between the alpha-to-theta ratio and the MoCA (r=0.60 p<0.01), as well as between the peak frequency and the MoCA (r=0.56 p<0.01). There was a negative significant correlation between the center of gravity and the MoCA (r=-0.48 p=<0.01). No significant correlation between the mean imaginary part of coherency and MoCA was found in the theta band (r=-0.09 p=0.43) and alpha band (r=0.09 p=0.41). The imaginary part of coherency differed significantly in some electrode pairs in the theta and alpha band between patients with and patients without cognitive impairment. The multinomial logistic regression analyses resulted in five models with different explanatory variables. The model with center of gravity as explanatory variable showed the highest sensitivity (92%) and specificity (50%).

Conclusion: Lower Alpha-to-theta ratio, lower peak frequency, and higher center of gravity correlated significantly with poorer cognitive functioning during hospital admission in cardiac arrest survivors. These qEEG measures hold potential to add to prediction of cognitive functioning as individual explanatory variable or in combination with demographic and clinical parameters.

List of abbreviations

BROCA	Brain Outcome after Cardiac Arrest
EEG	electroencephalography
Icoh	imaginary part of the coherency
MoCA	Montreal Cognitive Assessment
MRI	magnetic resonance imaging
NPE	neuropsychological examination
PSD	power spectral density
qEEG	quantitative electroencephalography
ROC	receiver operating characteristic
ROSC	return of spontaneous circulation

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1. Introduction

In the Netherlands, approximately 17,000 people experience an out-of-hospital cardiac arrest each year [1]. The survival rate of cardiac arrest is 23% and has increased considerably over the last decades [1], [2]. This is in contrast to neurologic outcome, which has only improved slightly [3], [4].

During cardiac arrest, oxygen and nutrient supply to the brain is temporarily insufficient [3]. The brain is highly susceptible to interrupted blood flow due to high oxygen consumption and high metabolic demand [3]. Cardiac arrest is strongly associated with hypoxic brain injury and might lead to cognitive impairment [5], [6]. About half of all cardiac arrest survivors experience long-term cognitive impairment, which may influence their quality of life, daily activities, and participation in society [6], [7]. All cognitive domains can be affected, with attention, memory, and executive functioning being reported most often [5], [6].

Although awareness of cognitive impairment in patients after cardiac arrest has increased, treatment is still mainly focused on cardiac care. To improve long-term outcome after cardiac arrest, treatment should also focus on neurological damage [8]. Cognitive rehabilitation is effective in patients with cognitive impairment caused by conditions such as stroke or traumatic brain injury [5], [9]. During this rehabilitation, they learn how to cope with cognitive impairment [5], [9]. In addition, patients learn how to compensate for cognitive limitations in order to participate in society [5]. Since cognitive rehabilitation is effective in these patients, it could also have beneficial effects on cardiac arrest survivors. To determine which patient might profit from this rehabilitation, early recognition of cardiac arrest survivors at risk for developing long-term cognitive impairment is important. Particularly since cognitive functioning recovers most during the first three months after cardiac arrest [6].

To date, early predictors for long-term cognitive functioning are not available yet. Possible predictors might be demographic parameters and clinical factors. Biochemical markers, such as neuron-specific enolase, in combination with neurologic examination and demographic parameters have provided valuable information about short-term neurological outcome [10]. Furthermore, biochemical markers, coma duration, and clinical measures were associated with long-term cognitive functioning in cardiac arrest survivors [11]–[13].

In Alzheimer’s or Parkinson’s disease, quantitative electroencephalography (qEEG) measures correlate with cognitive impairment and predict future cognitive deterioration [14]–[18]. Specifically, measures reflecting slowing of the dominant frequency and desynchronization of neural activity are associated with cognitive decline [14]–[18]. These measures can be derived from spectral and functional connectivity analyses. Given the potential of qEEG measures to predict cognitive functioning in Alzheimer’s or Parkinson’s disease, these measures hold potential to predict cognitive functioning in cardiac arrest survivors.

This thesis aimed to identify qEEG measures associated with cognitive impairment in cardiac arrest survivors. These exploratory analyses will serve as a first step toward a multimodal prediction model. The primary goals of this thesis were (1) to study associations between measures derived from power spectral analysis or global functional connectivity measures and cognitive functioning in patients after cardiac arrest; and (2) to study potential local alterations in functional connectivity in relation to cognitive functioning in patients after cardiac arrest. The secondary objective is to study predictive value of qEEG measures in addition to demographic and clinical parameters for predicting cognitive impairment during hospital admission in cardiac arrest survivors.

2. Methods

2.1 Study design

This master thesis was part of the ongoing Brain Outcome after Cardiac Arrest (BROCA)-prediction study, a prospective longitudinal cohort study on early prediction of long-term cognitive impairment in cardiac arrest survivors. Six Dutch hospitals participated in this study: Rijnstate (Arnhem), Medisch Spectrum Twente (Enschede), Maastricht Universitair Medisch Centrum Plus (Maastricht), Ziekenhuis Gelderse Vallei (Ede), Radboud universitair medisch centrum (Nijmegen), and Slingeland Ziekenhuis (Doetinchem). Patient inclusion started in November 2019 and is ongoing. In the BROCA-prediction study data were acquired during hospital admission and three, six, and twelve months after cardiac arrest. Clinical measures, magnetic resonance imaging (MRI), and electroencephalogram (EEG) were collected. Figure 1 visualizes an overview of the procedures of the BROCA-prediction study. For this thesis, we used demographic and clinical parameters, the EEG recording, and the Montreal Cognitive Assessment (MoCA) score obtained during hospital admission and at three and twelve months after cardiac arrest.

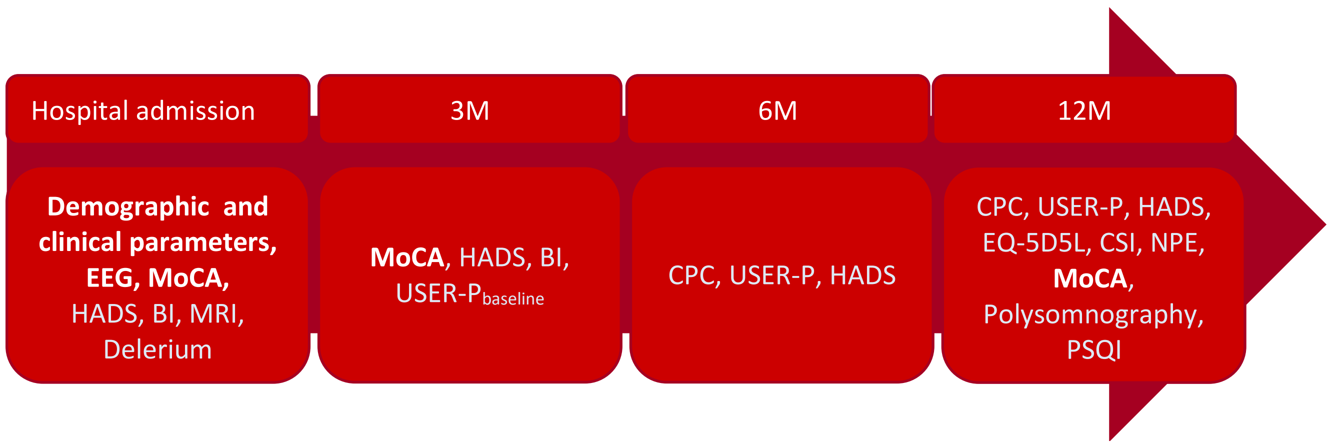

Figure 1 Overview of procedures for the BROCA-prediction study. The data used for this thesis were demographic and clinical parameters, the EEG recording, and the MoCA score obtained during hospital admission and at three and twelve months after cardiac arrest. BI: Barthel Index; CPC: Cerebral Performance Category; CSI: Caregivers Strain Index; EEG: electroencephalography; EQ-5D5L: EuroQol - 5 Dimensions – 5 Levels; HADS: Hospital Anxiety and Depression Scale; MoCA: Montreal Cognitive Assessment; MRI: Magnetic resonance imaging; NPE: neuropsychological evaluation; PSQI: Pittsburgh Sleep, Quality Index; USER-P: Utrecht Scale for Evaluation of Rehabilitation-Participation.

2.2 Participants

Patients after out-of-hospital cardiac arrest and cardiopulmonary resuscitation, admitted to the cardiology or cardiac care department, were eligible for the BROCA-prediction study. They were adults and had a Glasgow Coma Score higher than eight. Exclusion criteria were defined as: hanging or choking as primary cause of cardiac arrest, preexistent brain damage, a life expectancy of less than three months because of another medical condition, and insufficient knowledge of the Dutch language to fill out questionnaires. Furthermore, if cardiac arrest and resuscitation started in the ambulance, on the way to the hospital, with return of spontaneous circulation and consciousness upon arrival at the hospital, patients were not included.

2.3 Outcome

The primary outcome measure was cognitive functioning, defined by the MoCA score acquired during hospital admission. The MoCA is a validated screening tool for cognitive impairment in cardiac arrest survivors [19]. The score ranges from 0 to 30 and a MoCA score bellow 26 represents cognitive impairment [19]. In primary analyses, we used the continuous MoCA score acquired during hospital admission and at three and twelve months after cardiac arrest. In secondary analyses, the MoCA score was dichotomized as no cognitive impairment (MoCA≥26) and cognitive impairment (MoCA<26).

2.4 EEG recordings

EEG recordings were performed during hospital admission with different EEG recording systems, depending on the local hospital equipment, for details see Table A.1 in Appendix A. We used nineteen electrodes positioned according to the 10-20 system for each measurement. Electrode impedance was maintained below 5kΩ. The EEG was recorded in resting-state, and we asked the patient to relax and stay awake. The total duration of the EEG recording was twenty minutes during which the patient had to alter between eyes open and eyes closed. In total, we recorded five minutes of EEG with the eyes open and fifteen minutes with the eyes closed. During the recordings, an investigator took care of the signal quality. Furthermore, annotations were made during the recording in case of artifacts. If drowsiness was observed, the investigator gave a sound stimulus to keep the patient awake.

2.5 Epoch selection and preprocessing

We selected eyes closed, artifact-free segments for each patient by visual inspection. In addition to artifacts, sleep patterns recognized by the appearance of vertex waves and the disappearance of the alpha rhythm were not included in the current analyses. The minimum segment length was two seconds. Data preprocessing was performed offline using Matlab R 2020b. EEGs with a sampling frequency other than 256 Hz were resampled to 256 Hz with the Matlab resample function. We filtered the EEG data with a fourth-order Butterworth bandpass filter (1-40 Hz).

2.6 Spectral analysis

For the spectral analysis, the prefrontal and frontal electrodes were removed from the data to reduce the influence of eye movements. We estimated a power spectral density (PSD) for the remaining channels in a bipolar montage. Welch's method with a 512 sample Hanning window was applied to the data. Segments were split into two-second epochs (512 samples) with 50% overlap. Zero padding was applied to get a frequency resolution of 0.25 Hz. For every patient, we calculated one total PSD by taking the median of all PSDs in each channel and each epoch.

2.6.1 Alpha-to-theta ratio

We calculated the absolute power of the theta band (4-8 Hz) and alpha band (8-13 Hz) from the total PSD with the trapz function in Matlab. The alpha-to-theta ratio was calculated as

$$alpha - to - theta\ ratio = \frac{\alpha - \theta}{\alpha + \theta} \tag{1}$$

where α and θ are the absolute power calculated for the alpha band and theta band, respectively.

2.6.2 Peak frequency

The peak frequency was defined as the frequency where the power of the PSD was largest in the 4-13 Hz range. We used the findpeaks function in Matlab to identify this frequency. In low voltage EEGs (maximal value of the PSD in the frequency range of interest < 0.6 μV2/Hz), we preferred peaks in the alpha band to peaks in the theta band. In these EEGs, we defined the frequency with the highest power in the alpha band (8-13 Hz) as peak frequency. If no peak was found in the alpha band, the frequency with the highest power in the theta band (4-8 Hz) was selected as the peak frequency. By visual analysis of each PSD, the calculated peak frequency was reviewed. If the peak frequency did not meet the expected dominant frequency by visual analysis, the patient was excluded from this analysis.

2.6.3 Center of gravity

The center of gravity reflects the distribution of the EEG power in the anterior posterior and lateral direction. The center of gravity is normalized in the range -1 to 1, where -1 represents the posterior region of the brain and 1 the anterior part of the brain. Based on previous literature [20], [21] we expected diffuse neurological damage after cardiac arrest without differences in the lateral direction. We assumed that the correlation between cognitive functioning and the center of gravity only depends on the center of gravity in the anterior posterior direction. Therefore, we only calculated the center of gravity in this direction. We used raw EEG data without artifact handling. Eyes closed segments were extracted, and we removed the prefrontal electrodes. For each electrode, the frequency distribution was calculated according to the method described by van Putten (2008) [22]. Subsequently, we weighted the computed Fourier coefficients with its Euclidian distance from the Cz electrode in the anterior posterior direction. These results now reflected the center of gravity of the spectral power as function of the frequency. Eventually, the center of gravity of the dominant frequency in the frequency range 4-13 Hz was used for further analyses.

2.7 Imaginary part of coherency

Coherency determines the linear relationship between two EEG channels [23]. For this analysis, we used the filtered eyes closed artifact-free segments. Welch's method with a 512 sample Hanning window was applied to the data. Segments were broken down into two seconds epochs with 50% overlap. We applied zero padding to the data to acquire a frequency resolution of 0.25Hz. Coherency is defined as

$$Coherency = \frac{S_{xy}(f)}{\sqrt{S_{xx}(f)S_{yy}(f)}} \tag{2}$$

where S_{xy} is the cross-spectral density between signal x and y, and S_{xx} and S_{yy} are the Fourier transformations of signal x and y, respectively. We calculated the coherency for the theta band (4-8 Hz) and the alpha band (8-13 Hz). Brain activity of a single source in the brain can be measured at multiple electrodes on the scalp. Therefore, coherency is influenced by volume conduction and should be interpreted with care. We decided to ignore the real part of the coherency and isolate the imaginary part of the coherency (Icoh). This imaginary part is insensitive to volume conduction artifacts [23], [24]. Values of Icoh range from 0 to 1. No coherence between two signals is represented by a value of 0 and a value of 1 represents maximal coherence.

2.8 Statistical analysis

Variables were tested for normality by histograms and Q-Q plots. Data were represented as mean ± standard deviation in case of normal distribution. Non-normal distributed data were reported as median with interquartile ranges. Correlations between the MoCA score and qEEG measures were assessed using Pearson's correlation coefficient.

We compared the Icoh of patients with cognitive impairment and patients without cognitive impairment on a group level. For each electrode pair in the theta and alpha band, the difference in Icoh between both groups was tested with a Mann Whitney-U test. For each electrode pair that differed significantly, the correlation between the Icoh and continuous scores of the MoCA was assessed using Pearson's correlation coefficient. Electrode pairs with a correlation coefficient <0.10 were omitted since this relationship is negligible [25].

Multinomial logistic regression analyses were performed to determine the predictive value of qEEG measures in addition to demographic and clinical parameters for predicting cognitive impairment during hospital admission. The dependent variable was the MoCA score obtained during hospital admission dichotomized as cognitive impaired (MoCA<26) and no cognitive impairment (MoCA≥26). The independent variables included were age, gender, delay to start resuscitation, time to return of spontaneous circulation (ROSC), and the qEEG measures with a significant correlation with cognitive functioning during hospital admission. A backward stepwise approach was used based on likelihood ratio test statistics. We started with a full model and eliminated the variable with the least significant p-value during each step. This continued until the p-values of all included variables were ≤0.10.

We used five-fold cross-validation to validate our model. The data were randomly divided into five groups. For each fold, one group was used as test set, while the other four groups were considered as training sets. In each fold, a candidate model was developed. We aimed to reach high sensitivity (>80%) [25], minimizing the number of false negatives. A low number of false positives was less important because patients without cognitive impairment will not experience negative consequences from cognitive rehabilitation. However, high specificity is desired for clinical applicability. We aimed for the highest specificity with a sensitivity of >80%. The performance of the candidate models was evaluated based on the receiver operating characteristics (ROC) curve.

All statistical analyses were performed using IBM SPSS statistics 27 and Matlab R 2020b. P-values <0.05 were assumed statistically significant.

3. Results

3.1 Demographic and clinical characteristic

We included 77 patients in this study from the currently 92 patients included in the BROCA-prediction study. A flow diagram is provided in Figure 2. In thirteen patients, no EEG recording was available. Eight patients were included in Slingeland Ziekenhuis and Gelderse vallei. These hospitals did not perform an EEG after patient inclusion. In one patient, another EEG recording protocol was used. We needed more information before we could analyze this EEG. This information was not available at the time of the analyses. Three patients did not give their consent for the EEG recording, and one patient did not have an EEG recording due to logistic limitations. Table 1 shows patients characteristics of the included patients. There was a male predominance in this study. Mean age was 61 years. The median delay from cardiac arrest to start resuscitation was 0 minutes and the median time to ROSC was 10 minutes. There were no significant differences in baseline characteristics between patients with cognitive impairment (MoCA<26) and patients without cognitive impairment (MoCA≥26) during hospital admission.

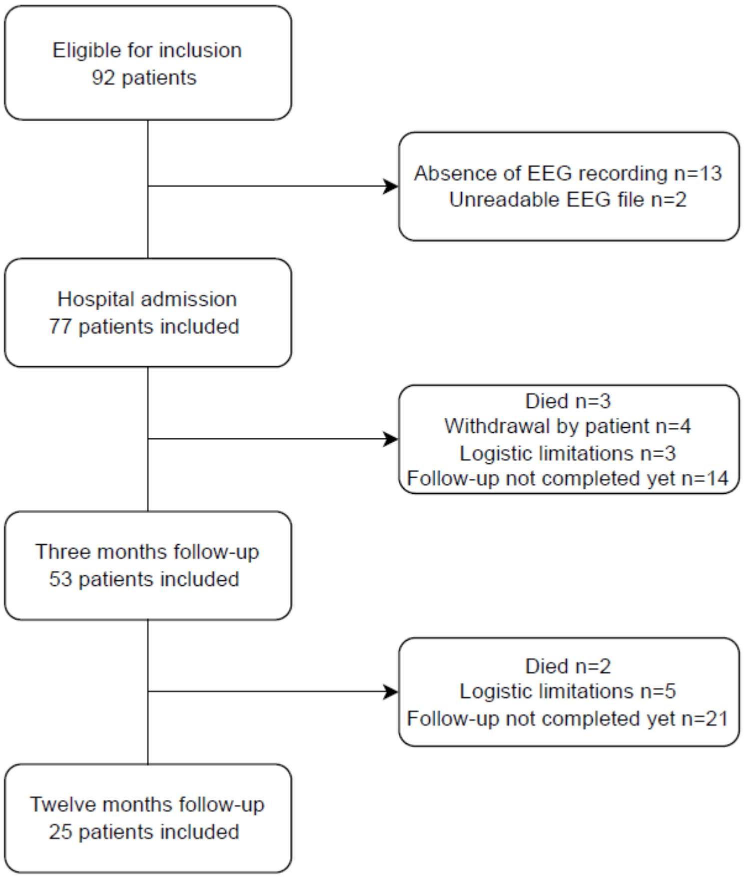

Figure 2 Flow diagram showing inclusion procedure of cardiac arrest survivors

Table 1 Patient characteristics and differences between patients with and without cognitive impairment based on the MoCA obtained during hospital admission.

Variable	All patients n=77	MoCA≥26 n=24	MoCA<26 n=53	p-value
Male sex, n (%)	67 (87)	22 (92)	45 (85)	0.42
Age (years), mean (SD)	61 (11)	58 (12)	63 (10)	0.07
Delay (min), median [IQR]	0 [0-1] n=73	0 [0-1] n=23	0 [0-2] n=50	0.19
Time to ROSC (min), median [IQR]	10 [8-15] n=72	10 [10-15] n=22	10 [8-16] n=50	0.37

3.2 MoCA score

The MoCA score was obtained during hospital admission and three and twelve months after cardiac arrest. The range of these scores and the number of patients with cognitive impairment for each time point are displayed in Table 2. The MoCA score obtained during hospital admission was administered within a median of 7 [4-12] days after cardiac arrest.

Table 2 MoCA scores obtained during hospital admission and three and twelve months after cardiac arrest

	Hospital admission n=77	Three months follow-up n=53	Twelve months follow-up n=25
MoCA score, min-max	7-29	19-29	20-30
Patients with cognitive impairment, n (%)	53 (69)	18 (34)	9 (36)

3.3 Spectral analysis

The median included number of artifact-free epochs was 14 [8-22] and had a length varying from 543 to 152615 samples. Figure B.1 in Appendix B depicts two examples of a PSD.

Figure 3 shows the correlation between the alpha-to-theta ratio and the MoCA score obtained during hospital admission. We found a significant positive correlation between the alpha-to-theta ratio and the MoCA score ($r=0.60$ $p<0.01$). In most patients, a negative alpha-to-theta ratio was associated with cognitive impairment. The correlation between the alpha-to-theta ratio and the MoCA score three months after cardiac arrest was significant ($r=0.28$ $p=0.04$), Figure C.1 Appendix C. The correlation between the alpha-to-theta ratio and MoCA score obtained twelve months after cardiac arrest was not significant ($r=0.04$ $p=0.84$), see Figure C.2 in Appendix C.

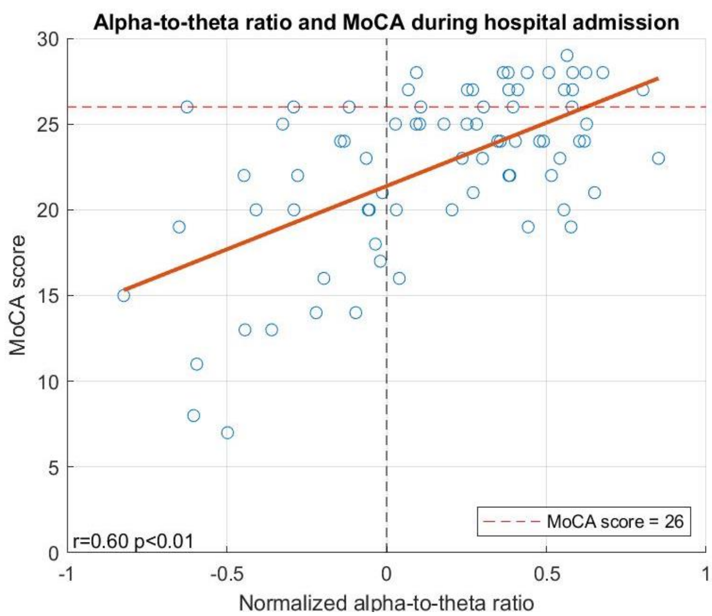

Figure 3 Correlation between the alpha-to-theta ratio and the MoCA score obtained during hospital admission. The dashed line in red represents the threshold of the MoCA score. The solid red line shows the trendline. We found a significant positive correlation (r=0.60 p<0.01). In most patients, a negative alpha-to-theta ratio was associated with cognitive impairment.

The correlation between the peak frequency and the MoCA score obtained during hospital admission is visualized in Figure 4. We excluded four patients from this analysis because their calculated peak frequency did not meet the dominant frequency determined by visual inspection. There was a significant positive correlation between the peak frequency and MoCA score during hospital admission ($r=0.56$ $p<0.01$). Peak frequency in the theta band (4-8 Hz) was associated with cognitive impairment in most patients. Figures C.1 and C.2 in Appendix C show the correlations between the peak frequency and the MoCA score at three months ($r=0.07$ $p=0.64$) and twelve months ($r=0.03$ $p=0.90$) after cardiac arrest.

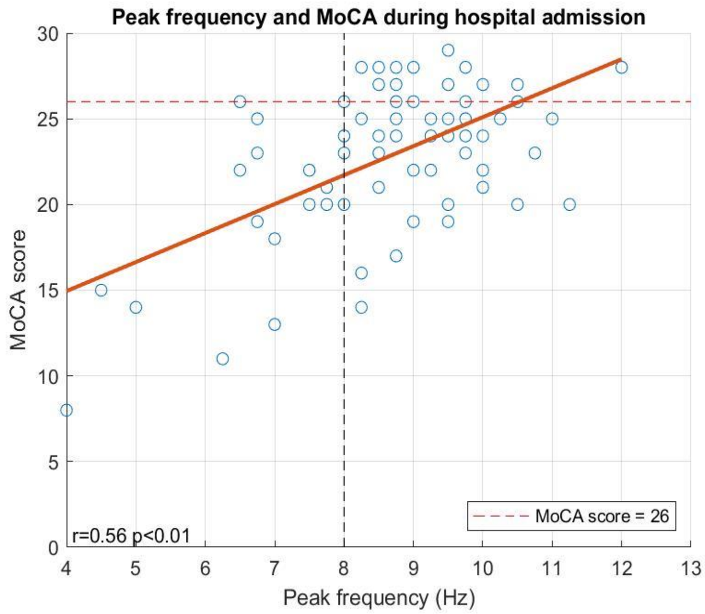

Figure 4 Correlation of the peak frequency and the MoCA score obtained during hospital admission. The dashed line in red represents the threshold of the MoCA score. The solid red line shows the trendline. We found a significant positive correlation (r=0.56 p<0.01). In most patients, a peak frequency in the theta band (4-8 Hz) was associated with cognitive impairment.

The correlation between the center of gravity and MoCA score obtained during hospital admission is presented in Figure 5. We found a significant negative correlation (r=-0.48 p<0.01) between these parameters. Center of gravity values close to zero were associated with cognitive impairment. We did not find significant correlations between the center of gravity and MoCA score three months (r=-0.14 p=0.33) and twelve months (r=0.05 p=0.82) after cardiac arrest. Figure C.1 and C.2 in Appendix C present these correlations.

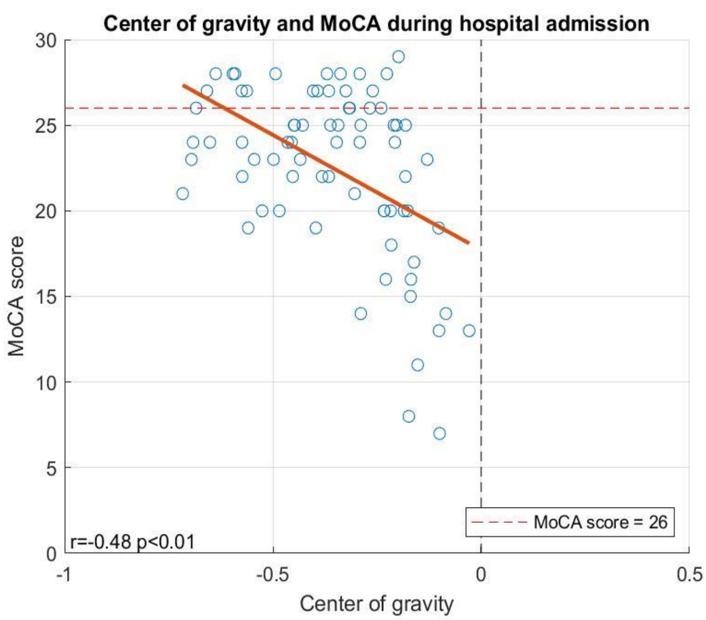

Figure 5 Correlation between the center of gravity and the MoCA score acquired during hospital admission. The dashed line in red represents the threshold of the MoCA score. The solid red line shows the trendline. We found a significant negative correlation (r=-0.48 p=<0.01). Center of gravity values close to zero were associated with cognitive impairment.

3.4 Imaginary part of coherency

No significant correlation was found between the averaged Icoh of the theta band and the MoCA score obtained during hospital admission (r=-0.09 p=0.43). We also did not find a significant correlation between the averaged Icoh of the alpha band and the MoCA score obtained during hospital admission (r=0.09 p=0.41). These results are shown in Figure D.1 in Appendix D.

Upon investigating local differences in Icoh in patients with cognitive impairment and patients without cognitive impairment, we did find significant differences in electrode pairs, see Figure 6. The Icoh in the theta band showed significant differences in fourteen electrode pairs, see Table E.1 in Appendix E. We found an increased Icoh in patients with cognitive impairment compared with patients without cognitive impairment. Twelve electrode pairs had a Pearson's correlation coefficient ≥0.10, see Figure 6a. We found nineteen electrode pairs with significant differences in Icoh between both groups in the alpha band, see Table E.2 Appendix E. Patients with cognitive impairment had lower Icoh compared with patients without cognitive impairment. Twelve electrode pairs had a Pearson's correlation coefficient ≥0.10, see Figure 6b.

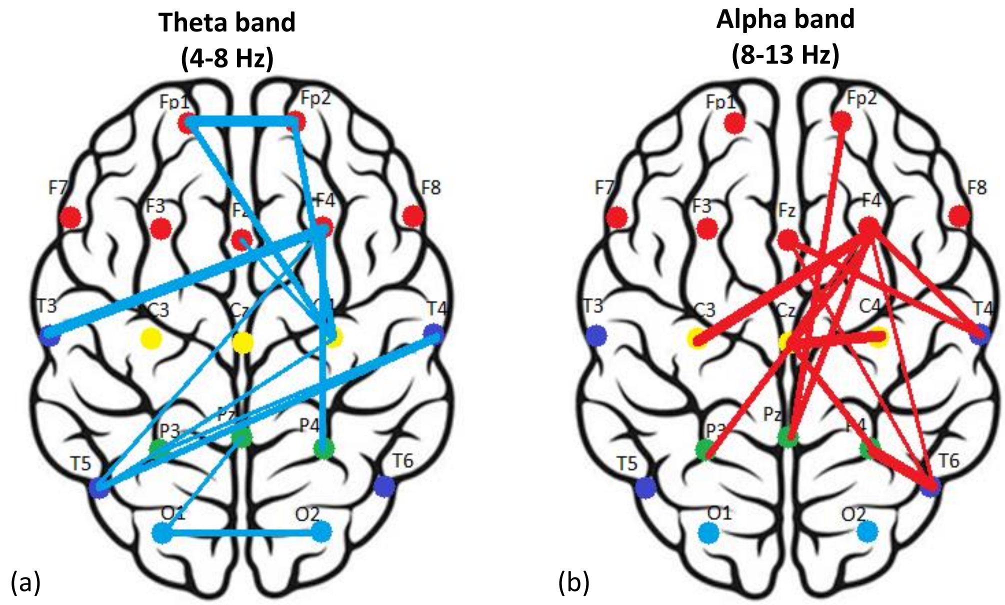

Figure 6 Electrode pairs with significant differences in Icoh between patients with cognitive impairment and patients without cognitive impairment for eyes-closed condition. Only electrode pairs with Pearson's correlation coefficient ≥0.10 are visualized. Blue lines indicate an increased Icoh in patients with cognitive impairment. Red lines indicate a decreased Icoh in patients with cognitive impairment. Thicker lines represent lower p-values. The exact p-values and correlation coefficients are summarized in Appendix E. In the theta band (4-8 Hz) (a) twelve electrode pairs showed significant differences between both groups. We found an increased Icoh in patients with cognitive impairment. In the alpha band (8-13 Hz) (b) twelve electrode pairs differed significantly between both groups. We found a decreased Icoh in patients with cognitive impairment.

3.5 Logistic regression model

The qEEG measures included in these analyses were alpha-to-theta ratio, peak frequency, and center of gravity. Five different candidate models were created during the folds, containing qEEG measures as explanatory variables with and without demographic parameters. Table 3 presents the results of the backward logistic regression analyses based on the likelihood ratio test statistics. The sensitivity and specificity of each candidate model are also shown in Table 3. The candidate model of the first fold, with center of gravity as explanatory variable, showed the highest sensitivity 92%, and specificity 50%. Figure 7 shows the ROC curves for each candidate model with corresponding area under the curve values. The candidate model of fold two reached the highest area under the curve, 0.72. The candidate model of fold five had the lowest area under the curve, 0.43.

Table 3 Multinomial logistic regression analyses with candidate models created during each fold and corresponding sensitivity and specificity.

Fold	Parameter	Regression coefficient	P-value *	Sensitivity (%)	Specificity (%)
1	Intercept	2.3	<0.01	92	50
	Center of gravity	4.6	0.02		
2	Intercept	-2.2	0.32	82	50
	Age	0.1	0.12		
	Ratio	-2.3	0.04		
3	Intercept	8.2	0.01	88	25
	Time to ROSC	-0.1	0.05		
	Peak frequency	-0.5	0.12		
	Center of gravity	5.8	0.21		
4	Intercept	-5.2	0.06	82	20
	Age	0.1	0.02		
	Ratio	-2.5	0.05		
5	Intercept	3.1	<0.01	86	14
	Delay	0.5	0.14		
	Time to ROSC	-0.1	0.06		
	Ratio	4.7	0.01		

* P-values based on Wald test

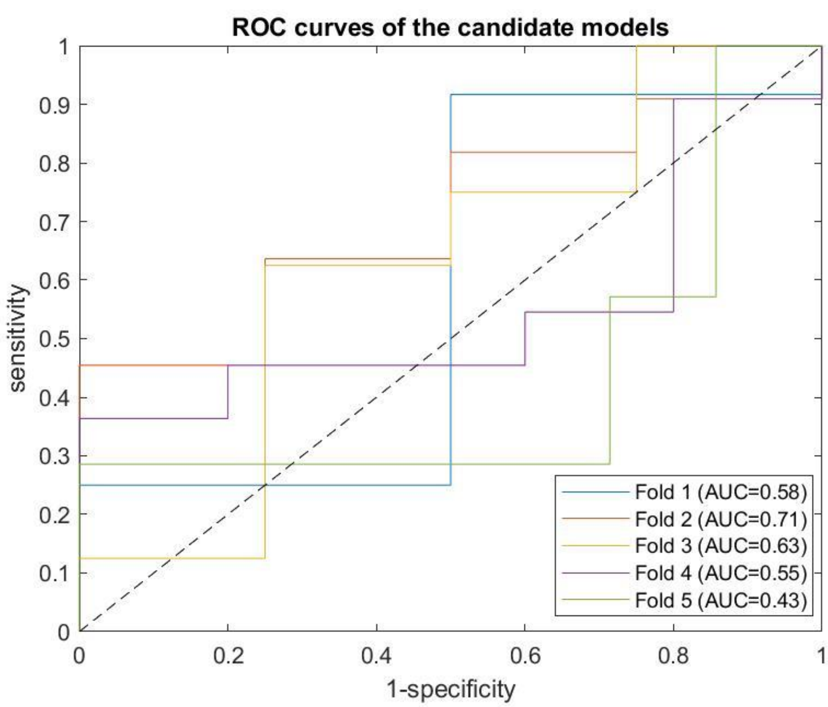

Figure 7 Receiver operating characteristics curves of the candidate models created during the five-fold cross-validation. The included explanatory variables in each model are presented in Table 3.

4. Discussion

In 77 cardiac arrest survivors, we analyzed the correlation between qEEG measures and early cognitive functioning examined with the MoCA score during hospital admission. We found a significant positive correlation between the alpha-to-theta ratio and this MoCA score as well as between the peak frequency and this MoCA. A significant negative correlation was found between the center of gravity and the MoCA score. We did not find a significant correlation between this MoCA score and the averaged Icoh of the theta and alpha band. The Icoh of electrode pairs compared on group level did show significant results. In both the theta and alpha band, we found twelve electrodes with a significant difference in Icoh between patients with cognitive impairment and patients without cognitive impairment. The significant results from the spectral analysis suggest that negative alpha-to-theta ratio, peak frequency in the theta band, and a center of gravity value close to zero were associated with cognitive impairment.

To the best of our knowledge, this is the first study to assess correlations between qEEG measures and cognitive functioning in cardiac arrest survivors. We compared our results with previous literature on Alzheimer's and Parkinson's disease. These are neurological diseases characterized by cognitive impairment. Several studies compared qEEG measures and cognitive functioning in these patients. We found a positive significant correlation between alpha-to-theta ratio and cognitive functioning. Cognitive impairment was associated with a negative alpha-to-theta ratio. This finding is in line with previous literature. Multiple studies stated that slowing of the EEG is associated with cognitive decline in Alzheimer's and Parkinson's disease [15]–[17], [26]. The peak frequency showed a positive significant correlation with cognitive functioning. Patients with a peak frequency in the theta band often showed cognitive impairment. This matches the results observed in the data included in the review on Parkinson's disease [14]. The authors concluded that a decreased peak frequency was correlated with cognitive impairment and could predict future deterioration. In addition, we found a significant negative correlation between cognitive functioning and center of gravity. Anteriorization of the center of gravity was found in patients with cognitive impairment. The shift in center of gravity is in accordance with previous findings in patients with Alzheimer's disease [27].

We did not find a significant correlation between the averaged Icoh in the theta band and cognitive impairment, and the averaged Icoh in the alpha band and cognitive impairment. Our results are in line with results from previous literature. Musaeus and colleagues compared averaged Icoh in patients with Alzheimer's disease, mild cognitive impairment, and healthy controls [24]. They did not find significant differences in Icoh between these patients.

In contrast, we did find significant differences in Icoh between patients with and without cognitive impairment in specific electrode pairs. However, these results should be interpreted with caution since there is no method to quantify or assess functional connectivity [28]. We found an increased Icoh in patients with cognitive impairment in the theta band. This result is in line with the results from the study in patients with Alzheimer's disease, mild cognitive impairment, and healthy controls [24]. However, they found an increase in the Icoh primarily in the posterior electrodes, which was not found in our results. In the alpha band, we found a decreased Icoh in patients with cognitive impairment. This is in contrast with the results from Museaus and colleagues [24]. They presented an increased Icoh in the alpha band between the frontal electrodes in both patients with Alzheimer's disease and mild cognitive impairment.

It is striking that we found significant correlations between spectral analysis measures and cognitive functioning but not between global connectivity measures and cognitive functioning. This discrepancy might be attributed to the influence of methodological choices on functional connectivity outcomes [29]. We tried to base our methodological choices on previous literature. However, literature about correlations between functional connectivity analyses and cognitive functioning is marginal [24]. This is in contrast to literature about spectral analysis. Numerous studies reported correlations between cognition and EEG spectral analysis, and it is a widely accepted principal analysis in neuroscience [30].

Another possible explanation for the difference in correlations between both analyses and cognitive functioning might be our choice of functional connectivity measure. Coherence is a popular measure for functional connectivity but is affected by volume conduction [31]. The effect of volume conduction can be avoided by examining the imaginary part of the coherence [31]. However, this imaginary part can be very small [29]. This might have led to missed interactions.

Strengths of this study include the broad patient population, including patients of all ages. We found cognitive impairment in 69% of the patients during hospital admission, in 34% of the patients three months after cardiac arrest, and in 36% of the patients twelve months after cardiac arrest. Although the results twelve months after cardiac arrest should be interpreted with care due to the small patient population, these results are in accordance with findings in previous literature. In the systemic review of Moulaert and colleagues [6], they stated that 42%-50% suffered from long-term cognitive impairment after cardiac arrest. In addition, they presented that cognitive functioning recovers most during the first three months after cardiac arrest [6]. Our patient population is a good representation of cardiac arrest survivors, which improves the generalizability of our results. Furthermore, we found strong significant correlations between the qEEG measures of the power spectral analysis and the MoCA score obtained during hospital admission. This confirms the potential of these measures to predict cognitive functioning after cardiac arrest.

This study had some limitations. First, some patients had a considerable difference between the day of the EEG recording and the day the MoCA was acquired. In most cases, the patient's clinical condition caused this considerable difference, due to for example long intensive care unit admission or the presence of delirium in the patient. Delirium is common for cardiac arrest survivors and is characterized by global cognitive impairment [32], [33]. The most common EEG findings during delirium are slowing of the frequencies and disorganization of the EEG rhythm [33]. These findings influence the qEEG measures analyzed in this study. In patients with delirium, the MoCA was often postponed until the patient was mostly recovered. Delirium recovery goes hand in hand with improvement of cognitive functioning. Therefore, it might be possible that patients who had a delirium and a considerable number of days between the EEG recording and the MoCA score, scored higher than expected based on the qEEG measures. This might have led to patients classified as cognitive impaired while their cognition improved after recovery from delirium. However, classifying these patients as cognitive impaired increases the number of false positives and does not lead to a decrease in sensitivity. Moreover, we found strong significant correlations between the MoCA acquired during hospital admission and the spectral analysis measures. Therefore, the influence might be insignificant.

Secondly, the validation set created for the five-fold cross-validation was quite small. We included 77 patients in this study which resulted in validation sets containing 15 patients. In addition, there were only 24 patients without cognitive impairment. Each validation set included on average five patients without cognitive impairment. However, we have divided the dataset randomly so some validation sets might have included fewer patients without cognitive impairment. This may have led to unreliable results. Despite the small validation set, the model with the highest sensitivity and specificity included only center of gravity as explanatory variable. We should interpret these results with care, but we think qEEG measures hold potential to predict cognitive functioning.

4.1 Future perspectives

This study mainly focused on the correlation between qEEG measures and cognitive functioning during hospital admission. About half of the cardiac arrest survivors experience long-term cognitive impairment. For long-term cognitive functioning prediction, correlations between qEEG measures and long-term cognitive functioning should be explored. Before this can be studied in our cohort, more patients should complete the follow-up.

Furthermore, we used the MoCA score to predict cognitive functioning in cardiac arrest survivors. The MoCA is a validated screening tool for cardiac arrest survivors which provides information about global cognitive functioning [19]. The MoCA scores during hospital admission were in a wide range. However, the scores during the twelve months follow-up were in a small range. Therefore, it might be of added value to use the neuropsychological examination (NPE) for the prediction of long-term cognitive functioning. The NPE is an extended test for cognitive functioning compared to the MoCA and is already used in cardiac arrest survivors [34], [35]. This test has the advantage that it provides more detailed information about cognitive functioning compared to the MoCA. Therefore, it is possible that the NPE can distinguish smaller differences in cognitive functioning.

Two candidate models created with the five-fold cross-validation might perform overfitting. They contained too many explanatory variables for the included patients in each outcome group. To prevent overfitting, each outcome group should contain at least ten patients for each variable included in the model. We did not set this condition in our analyses since it was exploratory. However, for a reliable prediction model, this condition is essential and should be considered in future work.

Delirium is characterized by cognitive deterioration and has a high incidence in cardiac arrest survivors [32]. Tsui and colleagues [36] investigated the effect of delirium on long-term cognitive functioning. They concluded that the presence of delirium has a negative effect on cognitive recovery. We did not investigate the influence of delirium on cognitive functioning in our regression analysis. Given the high incidence in our patient population and the influence on cognitive recovery, future research should focus on the influence of delirium on cognitive functioning.

5. Conclusion

Lower Alpha-to-theta ratio, lower peak frequency, and higher center of gravity correlated significantly with poorer MoCA scores during hospital admission in cardiac arrest survivors. These qEEG measures hold potential to add to prediction of cognitive functioning as individual explanatory variable or in combination with demographic and clinical parameters. Before these measures can be used in a multinomial prediction model, the association between long-term cognitive functioning should be established.

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Appendix A – EEG recording systems

Table A.1 Overview of participating hospitals in the BROCA-prediction study and their EEG recording systems and the used period of each system.

Hospital	EEG recording system	Period in use
Rijnstate	Nihon Kohden system (VCM Medical, Leusden, the Netherlands)	November 2019- April 2021
Rijnstate	Neurocenter EEG recording system (Clinical Science Systems, Leiden, the Netherlands)	November 2019 – still in use
Rijnstate	Brain RT system (Micromed, Mogliano Veneto, Italy)	April 2021 – still in use
Medisch Spectrum Twente	Neurocenter EEG recording system (Clinical Science Systems, Leiden, the Netherlands)	September 2020 – still in use
Maastricht Universitair Medisch Centrum Plus	Brain RT system (Micromed, Mogliano Veneto, Italy)	November 2020 – still in use
Ziekenhuis Gelderse Vallei	EEG recordings are not performed in this hospital	
Radboud universitair medisch centrum	Brain RT system (Micromed, Mogliano Veneto, Italy)	July 2021 – still in use
Slingeland Ziekenhuis	EEG recordings are not performed in this hospital	

Appendix B – Results of the power spectral analysis

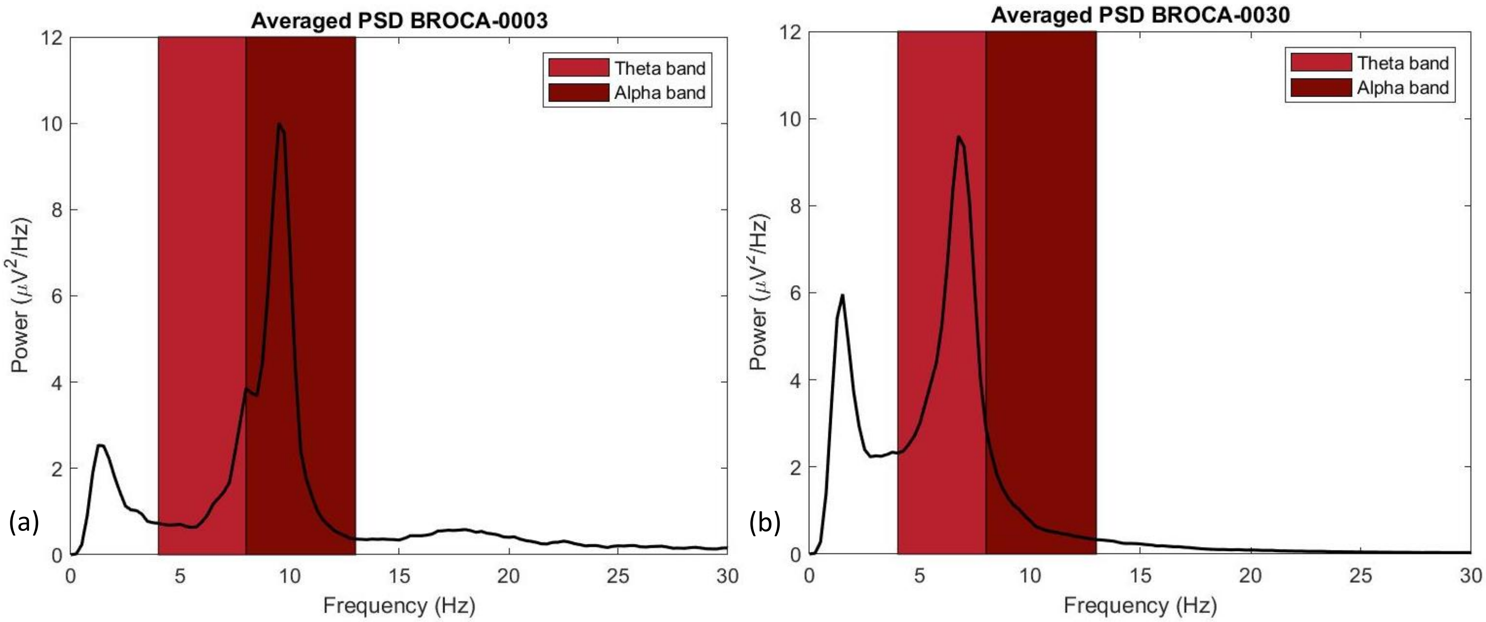

Figure B.1 Two examples of PSD. ***(a)*** *Shows the PSD of a patient with a MoCA score of 27 during hospital admission. The alpha-to-theta ratio is 0.556, the peak frequency is 9.50 Hz, and the center of gravity is -0.5747.* ***(b)*** *Shows the PSD of a patient with a MoCA score of 19. The alpha-to-theta ratio is -0.649, the peak frequency is 6.75 Hz, and the center of gravity is -0.1021.*

Appendix C – Correlations between qEEG measures and long-term MoCA scores

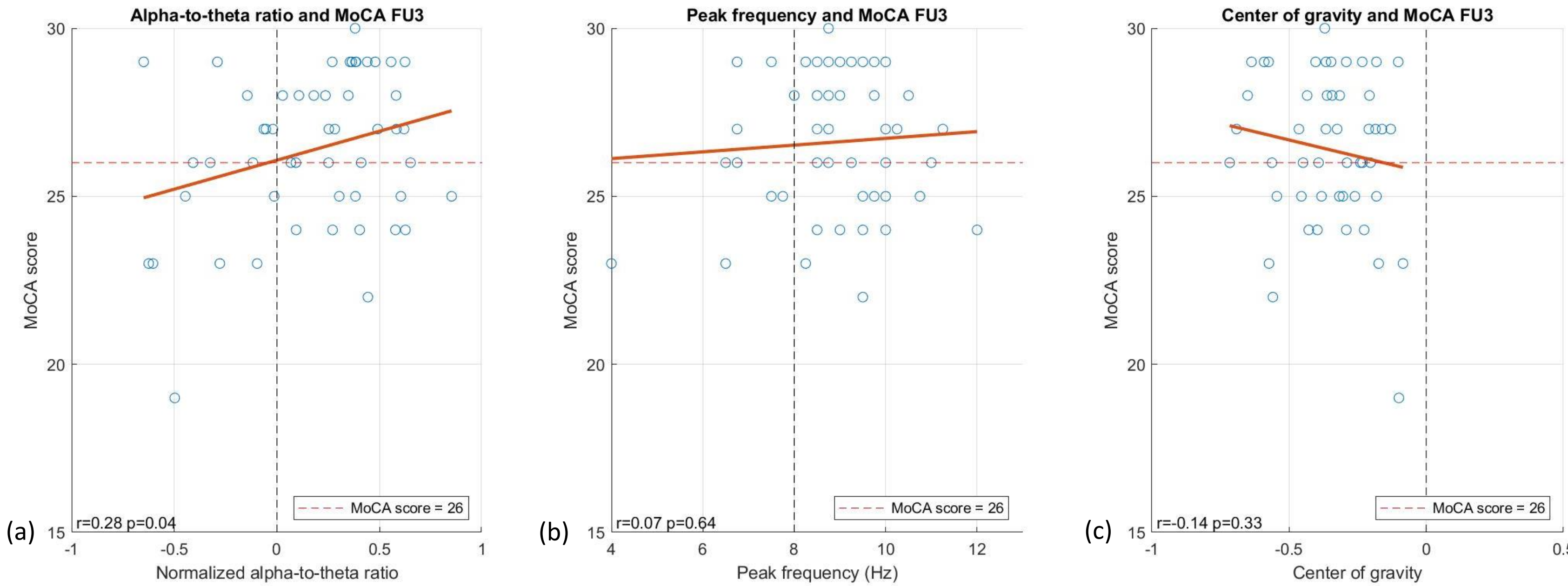

Figure C.1 Correlations between the qEEG measures and MoCA score obtained three months after cardiac arrest. The dashed line in red represents the threshold of the MoCA score. The solid red line shows the trendline. In the bottom left, the r and p values are shown. ***(a)*** *Visualization of the correlation between the alpha-to-theta ratio and the MoCA three months after cardiac arrest. We did find a significant positive correlation (r=0.28 p=0.04).* ***(b)*** *Correlation of the peak frequency and the MoCA three months after cardiac arrest. We did not find a significant correlation (r=0.07 p=0.64).* ***(c)*** *The correlation between the center of gravity and MoCA score three months after cardiac arrest. No significant correlation was found (r=-0.14 p=0.33).*

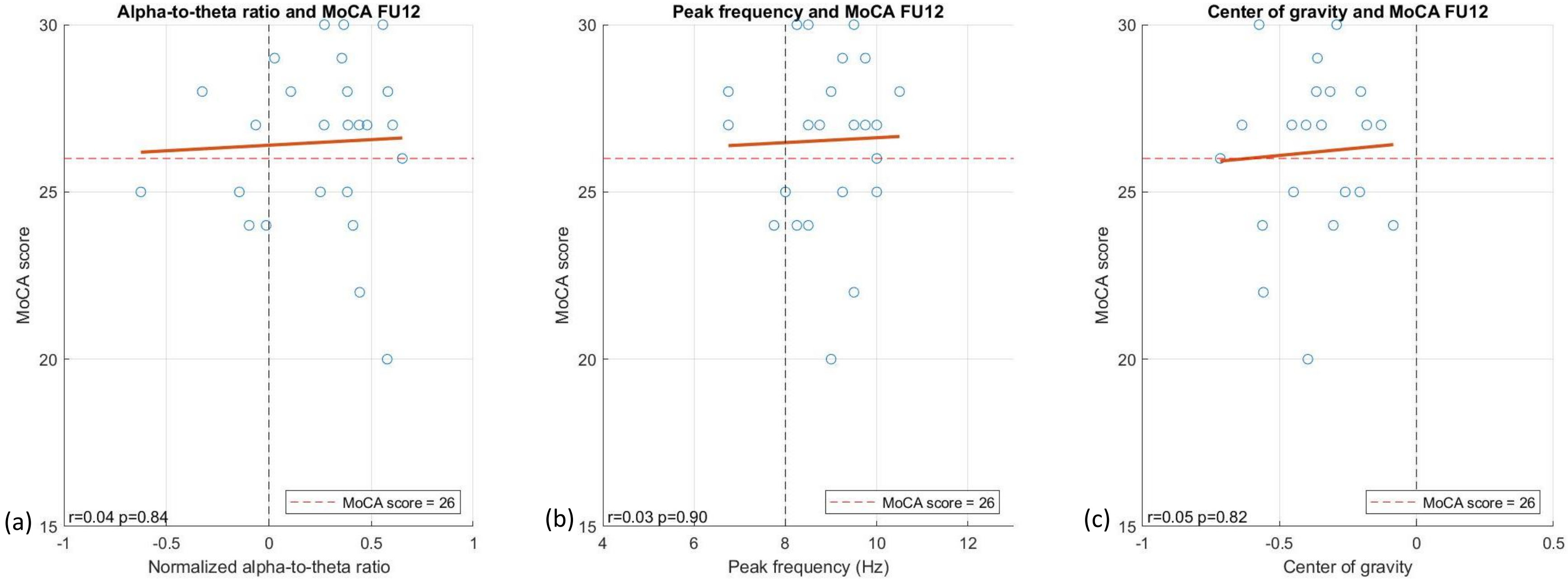

Figure C.2 Correlation between the qEEG measures and MoCA score obtained twelve months after cardiac arrest. The dashed line in red represents the threshold of the MoCA score. The solid red line shows the trendline. In the bottom left, the r and p values are shown. ***(a)*** *Visualization of the correlation between the alpha-to-theta ratio and the MoCA twelve months after cardiac arrest. No significant correlation was found (r=0.04 p=0.84).* ***(b)*** *Correlation of the peak frequency and the MoCA twelve months after cardiac arrest. The correlation was not significant (r=0.03 p=0.90)* ***(c)*** *The correlation between the center of gravity and MoCA score twelve months after cardiac arrest. We did not find a significant correlation (r=0.05 p=0.82).*

Appendix D – Correlations between averaged Icoh and MoCA score during hospital admission

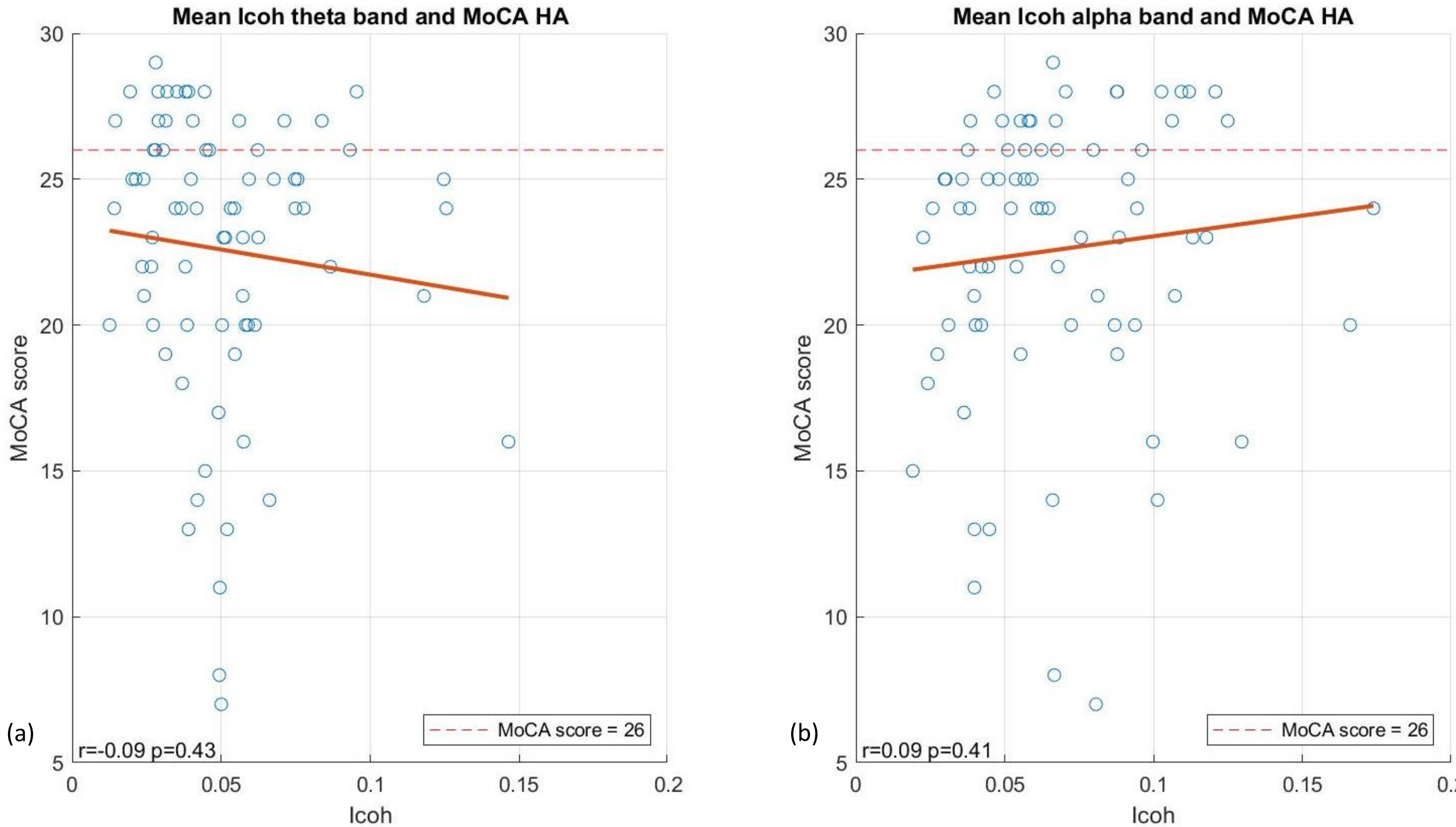

Figure D.1 Correlation between the averaged Icoh and MoCA score obtained during hospital admission. The dashed line in red represents the threshold of the MoCA score. The solid red line shows the trendline. In the bottom left, the r and p values are shown. (a) Visualization of the correlation between the averaged Icoh in the theta band (4-8 Hz) and the MoCA scores obtained during hospital admission. We did not find a significant correlation (r=-0.09 p=0.43). (b) Correlation of the averaged Icoh in the alpha band (8-13 Hz) and the MoCA score obtained during hospital admission. No significant correlation was found (r=0.09 p=0.41).

Appendix E – Significant levels and Pearson's correlation coefficients of the electrode pairs with significant differences in Icoh

Table E.1 Electrode pairs with significant differences in Icoh in the theta band between patients with and without cognitive impairment.

Electrode pair	P-value
O1-Pz	0.04
O2-O1	0.03
T5-Pz	0.05
C4-Fz	0.04
C4-T5	0.04
T4-P3	0.04
T4-T5	0.03
F4-P4	0.03
F4-T5	0.05
F4-T3	0.01
F8-Cz	0.02
Fp1-C4	0.02
Fp2-C4	0.02
Fp2-Fp1	0.01

Table E.2 Pearson's correlation coefficient of the electrode pairs in the theta band of which the Icoh differed significantly on a group level.

Electorde pair	Pearson's correlation	P-value
O1-Pz	-0.11	0.34
O2-O1	-0.17	0.15
T5-Pz	-0.07	0.56
C4-Fz	-0.13	0.27
C4-T5	-0.11	0.35
T4-P3	-0.11	0.33
T4-T5	-0.17	0.13
F4-P4	-0.16	0.16
F4-T5	-0.11	0.35
F4-T3	-0.11	0.33
F8-Cz	-0.04	0.72
Fp1-C4	-0.18	0.11
Fp2-C4	-0.20	0.08
Fp2-Fp1	-0.18	0.13

Table E.3 Electrode pairs with significant differences in Icoh in the theta band between patients with and without cognitive impairment.

Electorde pair	P-value
P4-Cz	0.02
T6-Fz	0.04
T6-P4	0.01
C4-Cz	0.01
C4-C3	0.04
T4-Pz	0.02
T4-Fz	0.03
T4-T6	0.04
T4-C4	0.04
F3-T5	0.02
F4-Pz	0.03
F4-Cz	0.05
F4-P3	0.03
F4-T5	0.04
F4-T6	0.05
F4-C3	0.01
F4-T4	0.02
Fp1-Pz	0.03
Fp2-Pz	0.03

Table E.4 Pearson's correlation coefficient of the electrode pairs in the alpha band of which the Icoh differed significantly on a group level.

Electorde pair	Pearson's correlation	P-value
P4-Cz	0.22	0.05
T6-Fz	0.14	0.23
T6-P4	0.24	0.03
C4-Cz	0.19	0.10
C4-C3	-0.05	0.69
T4-Pz	-0.05	0.67
T4-Fz	0.11	0.33
T4-T6	0.05	0.66
T4-C4	0.03	0.83
F3-T5	0.08	0.52
F4-Pz	0.19	0.11
F4-Cz	0.19	0.09
F4-P3	0.16	0.18
F4-T5	-0.06	0.64
F4-T6	0.17	0.14
F4-C3	0.27	0.02
F4-T4	0.22	0.06
Fp1-Pz	0.09	0.42
Fp2-Pz	0.12	0.30