

MEASUREMENTS OF COHERENCE IN EEG SIGNAL IN BRAZILIAN PEOPLE: A COMPARISON OF DIFFERENT CONSCIOUSNESS STATES

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Abstract

Critically ill patients admitted to intensive care units require special care and the early diagnosis of the possible outcome of this coma is clinically important. Electroencephalographic signals are collected daily in critically ill patients and can be used to aid in the early diagnosis of neurological pathologies in such patients. Therefore, this study aimed to quantitatively describe the coherence values measured by the EEG signal of Brazilian individuals. The first group with comatose patients (N = 75), favorable (to live) or unfavorable (dying) outcomes, and various etiology. The second group was made by neurologically normal people, named the control group (N = 100). In addition, a number of statistical comparisons were made in order to verify the difference in coherence behavior according to the levels of consciousness. The coherence index of the comatose group is smaller than the control group. Besides, different hospitalization results, living or dying, as well as different etiologies, may be associated with particular values of cerebral coherence. It was observed that the etiology of coma does not influence the measured values of coherence in terms of diagnosis due to brain death, which may become a biomarker of this outcome. Another important consideration was that neurologically healthy patients did not present high values of cerebral coherence at all electrodes, as seen in the temporal region of the brain.

Keywords: Coherence. Consciousness states. Electroencephalography.

1. Introduction

Some features of EEG may be associated with different clinical outcomes (Hofmeijer et al. 2014) so that most of the comatose patient EEGs presenting burst-suppression patterns with identical bursts were linked to death. Generally speaking, comatose patients may present different outcomes, both positive, like recovery, as negative, like brain death (Schomer and Silva 2011). In the last case, there are standard clinical procedures that might be performed to improve organ donation (Citerio et al. 2016; Westphal et al. 2016). Therefore, EEG records taken in comatose patients may help diagnosis and prognosis, thus leading to a better treatment.

Quantitative analysis in EEG signal processing is mainly performed at the frequency domain. For example, Lehembre et al. (2012) use spectral analysis to identify different conscious states, either the vegetative state (VS) or the minimum conscience state (MCS), based at three cerebral rhythms: Delta, Theta, and Alpha. The Delta rhythm power was higher for VS patients when compared with MCS patients, for all electrodes. On the other hand, Alpha rhythms presented opposite results when compared to Delta. Therefore, these conclusions are important because they may optimize clinical treatment.

Patients hospitalized in the Intensive Care Unit (ICU) need special care because they are vulnerable to several neurological pathologies, which can result in severe neural deficiencies (Herman et al. 2015). The electroencephalography (EEG) monitoring at ICU may improve visual perceptions of the signal abnormal morphology of the signal (Ebersole and Pedley 2003; Schomer and Silva 2011), for example at non-convulsive epileptic phenomena, allowing rapid medical interventions and improving the treatment of such patients (Vespa 2005; Cavalcanti et al. 2016).

For neuroscience, issues regarding symmetry involve the relationship of the right and left hemispheres of the brain (Hugdahl 2005). These hemispheres establish interconnections due to existing simultaneous activity between them; in consequence, the probability of both co-activation is higher in the absence of neurological abnormality. Therefore, neurology relates the level of cerebral symmetry with significant physiological roles, in order to detect pathologies. In fact, spectral features assessed by EEG in both hemispheres are similar for a neurologically normal person, including symmetry, which attains high amplitudes, although some rhythms present slight physiological asymmetry (Anghinah et al. 2005; Schomer and Silva 2011).

Therefore, right-left symmetry analysis is quite important for clinical decisions regarding comatose patients (van Putten 2007). Coherence analysis is a quantifier based on the EEG power spectrum of EEG. In the study of Tonner and Bein (2006), coherence was used to find out differences in the topographic distribution of Theta, Delta, Beta, and Alpha rhythms in elderly humans. In the study of Cavinato et al. (2014), coherence was employed to assess the functional relationships between cortical regions, considering patients with disorders of consciousness and in the vegetative state. Zubler et al. (2016) investigated symmetry levels between right and left hemispheres based on EEG coherence of comatose patients, pointing out different outcomes.

A retrospective study performed at the University Hospital of Federal University of Uberlandia (UH/FUU) between 2010 and 2013 identified around 128 patients, hospitalized in Adult ICU. This study pointed out that at least 22 patients had brain death. Using these data, our article aims to relate possible clinical outcomes (live or dead) with cerebral symmetry features, assessed by EEG signals. The cerebral symmetry analysis was related to different outcomes of comatose patient hospitalizations (Ramos 2017).

To the best of authors' knowledge, EEG coherence analysis of cerebral symmetry in comatose patients is very little, as shown in previous studies (Thatcher et al. 2001; Leon-Carrion et al. 2008; Xin et al. 2012; Lehembre et al. 2012; King et al. 2013; Cavinato et al. 2014; Sitt et al. 2014; Zubler et al. 2016; Xin et al. 2017; Zubler et al. 2017). In consequence, we did not find studies devoted to the quantitative characterization of coherence EEG signals associated with the Brazilian population. Therefore, we would like to compare coherence values in different situations, etiologies, or outcomes. For these reasons, this study is important due to the high number of patients analyzed (75), and the results will feed the very small literature on this subject.

2. Material and Methods

A retrospective study performed at UH/FUU between 2010 and 2013 (Ramos 2017) led to a total of 75 EEG signals from comatose patients. The inclusion criteria were comatose patients admitted at the adult ICU of UCH between 01/01/2010 and 31/12/2013, in the minimally conscious state (MCS). This group was divided into good or poor outcome. The good outcome (favorable outcome), named Alive, refers to all patients that presented good clinical recovery and were moved to another hospital sector for subsequent treatment. On the other hand, the poor outcome group was divided into Clinical death (CD), including patients who died for clinical reasons, like cardiac arrest, and Brain death (BD), referring to patients for which a diagnosis of brain death was established. These patients were also classified according to coma etiology. The more frequent etiologies were Stroke, Metabolic Coma (MC), and Traumatic Brain Injury (TBI). All other possible etiologies were grouped under the name "Others". By contrast, a control group was analyzed, which was previously developed in Ramos (2017). It is composed of 100 EEG recordings of healthy individuals, considering the following inclusion criteria: Neurologically normal person, without any prior neurological pathology, and that has not taken any neurological medicine in the last one year previous the recording.

All EEG signals processed in this work were collected by the EEG amplifier located at UH/FUU, using the standard 10-20 system of electrode placement, considering 20 EEG channels. The comatose EEG was

recorded at the ICU of this hospital as a consequence of the standard daily protocol of patient management, whereas the control group EEG was collected by our team at the neurological sector, at the same hospital. The ethics committee of our university released authorization for both data collection, according to protocols No. 369/11 (comatose group) and No. 54781615.6.0000.5152 (control group).

Two independent neurologists defined clinical neurological criteria to evaluate EEG signals. They analyzed all tracings and classified the best signals according to visual morphology. Subsequently, they selected ten different chronological epochs, which are free of artifacts derived from biological signals such as electrocardiogram and electromyogram, of each EEG signal. The time duration of each epoch was two seconds.

After the morphological analysis, all epochs were submitted to algorithm analysis, to verify the signal power behavior in the frequency range between 55 and 65 Hz, in order to minimize possible electromagnetic interference. If the time was rejected by the algorithm, the neurologist was asked to choose another section. Thus, all epochs analyzed in the present study were considered free of any noisy interference. Each one of the epochs was separated and grouped into matrices with 20 rows, following the number of electrodes; and M columns, which stands for the sample quantity within a segment, composed of two seconds of the signal.

The coherence (1) was evaluated considering all matrices generated. Notice that the coherence values may range from zero to one so that 'zero' indicates a complete absence of symmetry, and 'one' means the highest level of symmetry (Sörnmo and Laguna 2005).

$$C_{xy} = \frac{|S_{xy}(f)|^2}{S_{xx}(f)S_{yy}(f)} \quad (1)$$

Where in $S_{xx}(f)$ and $S_{yy}(f)$ refer to the power spectrum of signal x and y, respectively; $S_{xy}(f)$ refers to the cross-power spectrum of signals x and y.

The signals x and y in (1) represent pairs of electrodes. In the 10-20 system, there are eight pairs of symmetric electrodes, namely FP1-FP2, F7-F8, F3-F4, T3-T4, C3-C4, T5-T6, P3-P4, and O1-O2. In consequence, for each patient or individual, considering one pair of electrodes, ten calculus of coherence were performed, since ten different epochs were previously defined (Ramos et al. 2018).

Coherence was estimated considering the standard neurological frequency range of 1 - 30 Hz (Schomer and Silva 2011), separated according to the following standard: Delta 1 to 3.5 Hz; Theta 3.5 to 7.5 Hz; Alpha 7.5 to 12.5 Hz and Beta 12.5 to 30 Hz (Freeman and Quiroga 2013).

Considering the huge amount of data under processing, descriptive statistical analysis was used to summarize information as the median and the standard deviation of the median of each quantity. These values were chosen because at least one index of variation coefficient (VC) was higher 30%, wherein VC means the ratio between standard deviation and mean (Daniel and Cross 2012).

The coherence values were calculated for each group, Alive, CD, BD, and control, considering all electrode pairs and all brain rhythms. The significance level used in all comparisons was $\alpha = 95\%$ (p -value < 0.05 indicates statistical differences). Median values were selected to summarize the coherence calculations since random behavior does not follow a Gaussian model. For that reason, the Wilcoxon Hypothesis Test (Corder and Foreman 2014) was selected to compare the different situations. This is a nonparametric test, for which the null hypothesis is that the values compared are equal. The significance level used was $\alpha = 95\%$ (p -value < 0.05 indicates statistical differences).

3. Results and Discussion

Table 1 contains the demographic information for the groups considered in this paper. The age of the comatose group is bigger than the control group. Another consideration is the amount of EEG records from each comatose subgroup, which is considerably small (the highest value is 42 contributions to the CD outcome) relative to the control group.

Table 1. Demographic information of the analyzed data.

Group	Etiology	N	N of Male Gender	Age (years)	Cerebral Death	
Comatose	Outcome Favorable (Alive)	Stroke	5	2	60,40 ± 10,60	-
		MC	5	4	40,20 ± 14,29	-
		TBI	11	8	29,9 ± 9,48	-
		Others	0	0	0	-
	Outcome Unfavorable (Death)	Stroke	11	6	63,1 ± 6,67	2
		MC	19	17	55,45 ± 15,84	3
		TBI	11	7	39,81 ± 16,72	2
		Others	13	8	43,53 ± 19,61	5
Control	-	100	49	24.5 ± 6	-	

* MC – Metabolic Coma. TBI - Traumatic Brain Injury. N – Amount of EEG signals.

The coherence values were estimated for Delta, Theta, Alpha, and Beta rhythms and, for all eight electrode pairs, not only for the comatose groups but also for the control group. Table 2 contains these results. The following comparisons between the coherence values were made: Alive and CD, Alive and BD, CD, and BD, Alive and Control, CD and Control, and BD and Control. Considering all these comparisons, about 93% of the p-values achieved were smaller than 0.05, indicating that regardless of the level of consciousness and outcome, there are significant differences between the values of coherences measured.

Table 2. Coherence values in percentage measured by coma outcomes, which can be Active, CD, or BD.

Pair	Delta				Theta			
	Control	Active	CD	BD	Control	Active	CD	BD
FP1-	68.9 ±	34.58 ±	30.76 ±	20.86 ±	69.52 ±	33.24 ±	32.86 ±	22.26 ±
FP2	25.39	24.6	24.08	22.22	21.43	22.96	22.02	18.96
F7-F8	19.46 ±	18.81 ±	21.73 ±	26.26 ±	18.65 ±	22.74 ±	19.04 ±	26.44 ±
	18.91	19.18	21.58	28.22	17.87	22.25	21.82	26.86
F3-F4	62.44 ±	39.71 ±	34.4 ±	28.82 ±	64.48 ±	38.54 ±	29.44 ±	29.82 ±
	22.38	26.66	25.47	25.33	19.84	22.42	23.57	20.88
T3-T4	20.7 ±	25.34 ±	26.46 ±	31.28 ±	14.73 ±	26.8 ±	22.52 ±	31.52 ±
	19.46	23.64	24.36	30.46	16.23	21.16	21.24	28.24
C3-C4	63.42 ±	45.9 ±	42.44 ±	28.32 ±	59.94 ±	40.29 ±	36.18 ±	26.86 ±
	20.85	24.96	26.67	28.5	19.65	22.66	24.29	25.21
T5-T6	33.09 ±	30.46 ±	28.22 ±	33.94 ±	22.87 ±	26.13 ±	26.48 ±	28.86 ±
	21.93	25.08	26.12	29.19	18.59	20.51	23.41	28.35
P3-P4	65.82 ±	54.9 ±	40.27 ±	33.59 ±	61.49 ±	43.87 ±	41.02 ±	22.43 ±
	22.18	25.68	26.88	27.57	21.3	25.53	25.32	26.77
O1-O2	68.28 ±	63.07 ±	46.5 ±	40.68 ±	63.46 ±	53.83 ±	40.7 ±	30.38 ±
	22.3	27.1	26.37	28.24	21.48	24.52	26.19	25.74
Pair	Alpha				Beta			
	Control	Active	CD	BD	Control	Active	CD	BD
FP1-	86.32 ±	34.58 ±	32.52 ±	24.11 ±	58.53 ±	30.02 ±	28.58 ±	22.15 ±
FP2	17.7	23.15	22.75	18.62	23.17	27.54	22.97	18.92
F7-F8	40.08 ±	21.99 ±	16.87 ±	25.21 ±	15.62 ±	21.47 ±	14.91 ±	20.21 ±
	25.05	22.25	19.92	26.93	16.74	22.43	17.42	26.66
F3-F4	76.86 ±	33.88 ±	29.07 ±	22.99 ±	46.26 ±	32.15 ±	24.85 ±	20.21 ±
	21.71	21.96	21.06	22.65	23.02	27.01	22.27	21.79
T3-T4	17.76 ±	25.68 ±	20.93 ±	32.08 ±	13.22 ±	29.67 ±	22.65 ±	25.94 ±
	18.47	22.65	19.49	25.22	14.79	27.85	23.5	25.63
C3-C4	55.57 ±	34.9 ±	33.01 ±	27.53 ±	31.6 ±	29.98 ±	29.23 ±	21.55 ±
	24.22	22.4	22.87	25.41	20.66	25.73	24.33	24.24
T5-T6	27.66 ±	25.47 ±	23.85 ±	28.82 ±	13.93 ±	23.29 ±	25.65 ±	20.94 ±
	22.39	18.88	22.61	25.43	15.41	23.81	23.69	24.95
P3-P4	58.27 ±	40.67 ±	37.96 ±	24.12 ±	38.35 ±	34.47 ±	33.36 ±	20.47 ±
	24.41	25.26	24.03	24.98	21.33	28.99	25.66	24.2
O1-O2	67.96 ±	44.7 ±	38.13 ±	26.48 ±	47.11 ±	34.19 ±	32.63 ±	22.86 ±
	22.7	24.41	24.46	25.97	21.3	27.45	25.9	24.4

* CD – Clinical Death. BD – Brain Death.

Based on the coherence results for the comatose group, considering besides a patient's outcomes, the etiology of this coma, the coherence values were represented in Figure 1. This picture has three graphics, a) to c), referring to the outcomes, and the etiologies. Graphics show the curve of coherence values for range 1 to 30 Hz for all electrode pairs analyzed, like a histogram. The coherence values measured in the Stroke etiology are statistically different from those obtained in the TBI etiology, considering both the Alive and the CD outcomes (p -value = 0.02; p -value = 0.003 respectively). This pattern was also observed when the coherence values obtained in the Stroke etiology with the MC etiology were compared for such outcomes (p -value = 0.01; p -value = 0.1 respectively). The coherence values measured in the TBI etiology were not different from the values obtained in the MC etiology, regardless of the outcome of the patient (p -value > 0.05). It is important to note that individuals who progressed from coma to brain death did not present a statistical difference of coherence values for any etiology and could conclude that in this situation the coherence values measured in the EEG signal are independent of the etiology.

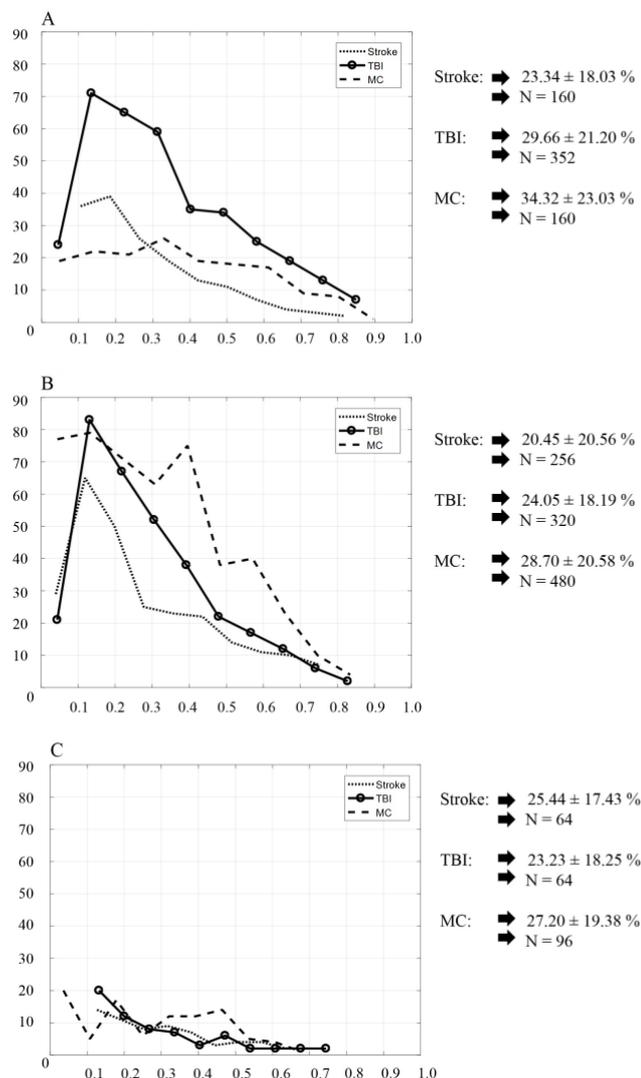


Figure 1. Behavior of coherence indices, in percentage, measured at all rhythms and pairs of electrodes, considering coma etiology and patient outcome. The short dashed line indicates the Stroke etiology. The continuous line indicates the TBI etiology. Finally, the broad dashed line indicates the MC etiology. A – outcome: alive; B – outcome: CD; C – outcome: BD. The values of mean and standard deviation obtained for each etiology are shown alongside each image, as well as the (N) count of the total values considered for the calculation, which can vary with the number of records analyzed in each case, influencing in the amplitude of the curves.

Quantitative aspects of comatose EEG, shown in Table 2, can be used for diagnostic purposes in the patient, as well as possible predictors of coma evolution. In a study (van Putten et al. 2004) carried out with 57 patients under stroke risk, cerebral power levels were estimated, and their amplitudes were inversely

proportional to frequency. It was also found that the symmetry was low. This result agrees with Table 2. On the other hand, Table 2 depicts that the symmetry value of the coma group is statistically different from the control one, regardless of the rhythm and/or the electrode pair. The range of values for the coma group varies between 14.91% (pair: FP1-FP2 of Beta rhythm; outcome: CD) and 63.07% (pair: O1-O2 of Delta rhythm; outcome: Alive), that is, most of the coherence values are below 50%. The control group presented values between 13.22% (pair: T3-T4 of Beta rhythm) and 86.32% (pair: FP1-FP2-T4 of Theta rhythm). In consequence, for the control group, coherence values are not always high, particularly for all temporal electrodes. Notice that Table 2 represents a simplified quantitative standard of neurological normality and abnormality associated with coma.

The study conducted by Koskinen et al. (2001) for neurologically normal individuals has shown that interhemispheric symmetry decreases with the degree of anesthesia. Similar conclusions were achieved in Wang et al. (2014), for which normal individuals under the anesthesia effect presented low amplitudes of inter-hemispheric coherence, mainly in the frontal and occipital cortical areas. In addition, EEG records of both patients with disorders of consciousness and normal individuals had been evaluated in Cavinato et al. (2014). This work highlighted that the coherence tied to the alpha rhythm at parietal regions of the control group was significantly higher than the comatose group. All these results agree with Table 2. For this reason, one may state that the coherence values tied to the control population are higher than those of the comatose one, in the absence of stimuli, except for the temporal regions. Additionally, the standard values of these coherences are higher for the comatose group. In King et al. (2013) it was concluded that anatomical lesions of patients in a vegetative state can lead to functional deficits in the communication between the thalamus and cerebral cortex, thus generating abnormal activity in the network of cerebral communication, which in turn may decrease interhemispheric symmetry, e.g., coherence.

Concerning the analysis of the comatose group, Table 2 shows that the coherence indexes calculated for each outcome are different. For example, in the Alive outcome, electrodes O1-O2 (in the Delta, Theta and Alpha rhythms) and P3-P4 (in Beta rhythm) presented the highest values of coherence. In the CD outcome, the highest values of coherence were identified in the P3-P4 and O1-O2 pairs, whereas, for the BD outcome, the T3-T4 pair yielded the highest coherence values (Theta, Alpha, and Beta rhythms). Considering all pairs of electrodes, the minimum coherence values were detected in the CD group, especially in the Beta rhythm.

In one study (Cavinato et al. 2014), patients in a vegetative state or minimally conscious state and a control group were evaluated. High values of coherence for the posterior Alpha rhythm were estimated for both groups. In contrast to the results of Table 2, in other study (Zubler et al. 2016) although most quantifiers presented significant statistical differences between each other for different outcomes, a high level of synchrony was assessed at comatose patients who died, including brain death.

Considering not only the outcome but also the etiology of the coma, it was noted that, for the Alive outcome, Figure 1a, considering the Stroke, TBI, and MC etiologies, coherence values vary between 23.34% and 34.32%. Results of these curves in Figure. 1a, were compared to each other, most of all values leading to significant differences (p -value > 0.05 , $\alpha = 95\%$). However, the etiologies Stroke and MC presented the most different coherence values (p -value > 0.005 , $\alpha = 95\%$). The behavior of these three curves is similar in the Alive outcome, and most of the measured values of coherence are located between 10% and 30%.

For the CD outcome, represented in Figure 1b, the coherence range is 20.45% to 28.7%. Notice that these values are different compared to the Alive outcome. The overall analysis of these figures points out that each etiology within this outcome presents a different coherence value when compared to each other (p -value < 0.05 ; $\alpha = 95\%$). Consider now just BD results in Fig. 1, (c), note that coherence range was from 23.23% to 27.20% and that the coherence values measured in each etiology are similar, indicating that for the outcome of brain death there is no distinction between coma etiologies.

In the study of Xin et al. (2012), considering patients with stroke, it is possible to associate high levels of symmetry between the left and right hemispheres of patients with unfavorable outcomes. This was also concluded in other study (Xin et al. 2017), which supposed patients suffering from a stroke. In view of the study of Leon-Carrion et al. (2008), performed in patients with minimal consciousness, and patients under severe neurocognitive disorder, no significant difference between the coherence of these groups was assessed. Therefore, it is not always possible to distinguish different types of conscious levels of comatose

patients by using cerebral symmetry. In one study (Thatcher et al. 2001), patients suffering from different kinds of cerebral lesions were analyzed, grouped into mild, moderate, or severe lesion degree. Coherence values could be associated with soft and hard trauma.

The neural responses of patients with disorders of consciousness, which were caused by different etiologies such as stroke, TBI, and MC; as well as healthy controls; were assessed in Cavinato et al. (2014). For unconscious patients, it was noted low values of coherence in the parietal regions for the Alpha rhythm. Conversely, high values of coherence were calculated in the parietal and frontal regions for the Theta rhythm. These findings agree with Table 2 and Figure 1. In consequence, after relating the results of the literature to the present study, it is clearly quite important to analyze patients with similar levels of consciousness, in order to achieve reliable results.

4. Conclusions

Findings of the present study, as well as the literature on the subject, point out that EEG recordings performed in critically ill patients are of extreme clinical relevance since their quantitative interpretation supports the diagnosis of disturbances of consciousness and prognosis of comatose patients. Coherence analysis can be used to quantitatively discriminate comatose EEG from control records, as well as comatose EEG with different outcomes and etiologies. Table 2 summarizes the values of brain symmetry obtained by coherence estimations, for comatose EEG signals, as well as for control recordings, emphasizing that such values are higher in the condition of neurological normality.

In this article, EEG examinations performed at early stages of the coma state of Brazilian patients (N = 75) were studied in a retrospective way and compared to a control group (N = 100), in order to assess whether quantitative analysis could be useful for prognostic and diagnostic purposes. In brief, one may conclude that coherence analysis can be used to quantitatively discriminate comatose EEG from control records, as well as comatose EEG with different outcomes and etiologies, as shown by statistical analysis.

Table 2 summarizes the mean coherence estimations for both comatose EEG signals, as well as for control recordings, emphasizing that such values are higher in the condition of neurological normality. This table defines a quantitative pattern characterizing normal and pathological contexts, which is quite important for clinical diagnostics, brain-machine interface, and rehabilitation purposes, disclosing important findings. The coherence is lower than 33% for all temporal and F7-F8 electrodes in normal individuals, which is a quite surprising result, pointing out that neurological normality does not lead to high amplitudes of coherence in all electrodes.

By analyzing the hospitalization outcomes of comatose patients, such as to live or dying, it is also possible to establish relevant remarks regarding the brain-death (BD) outcome. As etiologies are considered in the quantitative analysis, new insights can be derived. Statistical analysis of Figure 1 points out that quantitative results tied to TBI etiology and those to Stroke etiology are the most different ones, considering all electrodes and rhythms. However, in the context of patients with BD outcome, it is possible to note that not present a statistical difference of coherence values for any etiology and could conclude that in this situation the coherence values measured in the EEG signal are independent of the etiology.

In summary, the values of left-right cerebral coherence are distinct according to the coma etiology and to the hospitalization outcome. In this sense, future prospective studies should consider patients with similar etiologies and levels of consciousness. Particularly, the role of the standard deviation of the mean coherence should be investigated as a complementary quantifier since it is quite important to assess BD outcomes. In addition, other kinds of theories and quantifiers could be considered, in order to contribute to the clinical neurology and diagnoses of patients hospitalized in ICU settings.

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Conflicts of Interest: The authors declare no conflicts of interest.

Ethics Approval: Approved by Research Ethics Committee of Federal University of Uberlândia. Number: 369/11 (comatose group) and 54781615.6.0000.5152 (control group).

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