Consciousness transitions during epilepsy seizures through the lens of Integrated Information Theory

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Abstract

Consciousness is one of the most complex aspects of human experience. Studying the mechanisms involved in transitions and in different levels of consciousness is one of the greatest challenges of neuroscience. In this study we use a measure based on computing the integrated information using an autoregressive system (Φ_{AR}) to evaluate dynamic changes during consciousness transitions. This index is applied to an intracranial electroencephalography (iEEG) dataset collected from 6 patients that suffer from refractory epilepsy. These records were obtained during resting state and during the crisis. Networks outside epileptogenic regions were created in order to study the ΦAR index evolution when a crisis is detected. By using the Consciousness Seizure Scale (CCS) we show that changes on ΦAR are significantly correlated with changes in the reported states of consciousness.

1. Introduction

Consciousness is undoubtedly one of the fundamental aspects, perhaps the most crucial, of human experience. It has been the subject of extensive study for various reasons throughout the history of humanity, captivating the minds of philosophers, physicians, researchers, and other thinkers. Despite centuries of research, it remains a challenging and elusive topic. Having a reliable method for estimating the level of consciousness within a system carries significant implications in diagnostics, as demonstrated by Sitt *et al.*[1] In this specific case, they employed event-related potentials, frequency analysis, complexity, and connectivity analysis to investigate the effectiveness of these approaches in distinguishing various states of consciousness among comatose patients. These methods facilitated the examination of individual cases through single-electrode signals and the connectivity between two electrodes. However, they can't explain complex interactions involving more than two electrodes. In the last decade, a group of researchers has leveraged the advancement of technology and the increasing computational power to conduct experiments and test various theories using image and signal processing. Cutting-edge neuroimaging tools, such as functional magnetic resonance imaging (fMRI), electroencephalography (EEG), and magnetoencephalography (MEG), have allowed them to dive deeper into the neural underpinnings of consciousness. One of the most accepted theoretical frameworks used to study consciousness is the Integrated Information Theory (IIT) proposed by Guilio Tononi[2]. The theory suggests that consciousness is not a byproduct of processing information in the brain but an intrinsic property that emerges from the integration of information within a system. It also provides a way, the Φ index, to quantify the level of information integrated within a network, that is information that cannot be explained as the sum of the individual parts of the system. This index can be estimated from empirical data (i.e. intracranial electroencephalography - iEEG) using an empirical distribution as proposed by Barret et al.[3] This index (or some of its variations) was previously computed on EEG[4] and fMRI[5] recordings in humans, and ECoG recordings in monkeys[6] but it hasn't been computed on iEEG data from humans.

In this study, we examine transitions in consciousness level during epileptic seizures. The primary objective is to assess the robustness of the Φ index in detecting various states of consciousness. We computed the Φ_{AR} index using a collection of iEEG recordings obtained from six distinct patients who had undergone exploratory surgery to investigate epileptogenic zones. The Φ_{AR} index, a modification of Φ reliant on auto-regressive prediction error, was computed for non-Gaussian systems [3]. To determine changes in consciousness during an epileptic seizure, we computed $\Delta\Phi_{AR}$ by subtracting the baseline value from the index value obtained during the seizure. This $\Delta\Phi_{AR}$ is regarded as an indicator of the consciousness shifts occurring during such seizures. Concurrently, medical professionals employed the Consciousness Seizure Scale (CSS) index to assess the degree of consciousness loss (LOC) during each crisis [7], [8]. Using this, we established a correlation between $\Delta\Phi_{AR}$, computed from iEEG signals, and the CSS index as reported by the medical experts. To complement these findings, we also computed the mean shortest path and modularity. To ascertain the continued validity of the index within brain regions severely affected by epileptic crises, we selected electrodes from both epileptogenic and non-epileptogenic regions based on physicians reports, conforming two distinct groups: compromised and non-compromised. The following sections provide a comprehensive presentation of all materials, methodologies, and outcomes obtained from this research.

2. Materials and Methods

This study was approved by the Review Ethics Board of El Cruce Hospital, Buenos Aires, Argentina, according to the

Declaration of Helsinki. All patients were informed of the purpose and possible consequences of this study and signed

an ethical board-approved written informed consent. For this study we selected 6 adult patients with drug-resistant epilepsy candidates to surgery, in whom it was necessary the use of intracerebral electrodes (SEEG) for the studying of the epileptogenic zone. The inclusion criteria were patients in whom we could completely evaluate consciousness during seizures. All patients had a comprehensive evaluation including detailed medical record and neurological examination, neuropsychological testing, routine magnetic resonance image (MRI), scalp EEG and SEEG. SEEG was carried out as part of the patients' routine clinical care and informed consent was given in the usual way.

2.1 Consciousness Evaluation

We use the Consciousness Seizure Scale (CSS) for determining the loss of consciousness (LOC). The scale considers different features of conscious experience, delineating 8 criteria. All items were rated by two different epileptologists (NC and SK): items 1 to 7 can be scored 0 or 1, while the eighth item from 0 to 2, thus yielding a possible total score of 0 to 9. Higher scores indicate more severe loss of consciousness. Based on the total score, 3 groups were defined: without LOC (score ≤ 1), an intermediate LOC (score ranging from 2 to 5) and with profound LOC (score ≥ 6).

2.2 Electrode's implantation

Depth electrodes (Ad Tech) had: (a) 8 or 10 platinum contacts with 5- or 10-mm inter-contact center to center distance,

contact length of 2.4 mm and 1.1 mm diameter, or (b) 9 platinum contacts with 3 mm distance between the first and the second contact and 6 mm inter-electrode distance from the second to the last. Contact length was 1.57 mm and the electrode diameter was 1.28 mm. Electrodes were identified by a letter of the alphabet. There was no standard labeling for each location. Contacts within an electrode were usually identified with numbers beginning from the deepest (contact number 1, corresponding to the tip) to the base.

2.3 Intracranial electroencephalography recordings

SEEG signals were acquired using the software Cervello 1.04.200, sampled at 2000 Hz with bandpass filtering between

0.7 Hz and 200Hz. The seizure onset was identified by two epileptologists (NC and SK) through independent reviews.

The ictal onset was identified as initial SEEG changes, characterized by sustained rhythmic discharges or repetitive

spike-wave discharges that cannot be explained by state changes and that resulted in habitual seizure symptoms similar to those reported in previous studies. The seizure onset zone was defined as the contacts where the earlier ictal SEEG changes were seen.

2.4 Data Analisis

We obtained our results computing the Φ_{AR} index for the electrode signals. This index, proposed by Barret *et al.* in [3], allowed us to obtain an estimation of the integrated information using the empirical covariance matrices and skipping, in this way, the assumption that our data comes from a Gaussian system. The effective information is defined as

$$\phi_{AR}\left[X;\tau,\beta\right] = \frac{1}{2}log\left\{\frac{det\Sigma\left(X\right)}{det\Sigma\left(E^{X}\right)}\right\} - \sum_{k=1}^{2}\frac{1}{2}log\left\{\frac{det\Sigma\left(M^{k}\right)}{det\Sigma\left(E^{M^{k}}\right)}\right\} (1)$$

where *X* is the data matrix, *M* is a subset of *X* (partition), *E* is the residual in the regression on *X*, and E^M is the residual in the regression on *M*. Φ_{AR} is defined as the particularization of the integrated information for the bipartition $\{M^1, M^2\}$ that minimizes ϕ_{AR},

$$\Phi_{AR}\left[X;\tau\right] = \phi_{AR}\left[X;\tau,\beta^{min}\left(\tau\right)\right] (2)$$

where,

$$\beta^{min}(\tau) = arg_{\beta} min \left\{ \frac{\phi[X;\tau,\beta]}{L(\beta)} \right\} (3)$$

being L a normalization factor defined by,

$$L\left(\{M^1, M^2\}\right) = \frac{1}{2} logmin_k \left\{ (2\pi e)^{|M^k|} det\Sigma\left(M^k\right) \right\} (4)$$

where and β^{min} is the minimum $\phi_{AR,}$ defined in formula 2, for all {i,j} bi-partitions $\{M^i; M^j\}$, and L(β) is the normalization factor.

In order to compute the Φ_{AR} index evolution through time, we downsampled the EEG records to 200 Hz taking 1 sample out of 10. We z-scored each signal and then we applied a 50Hz notch filter to remove line noise. We used a bandpass filter to limit the signal's bandwidth between 4 Hz and 20 Hz. We selected 6 different electrodes from brain regions that were classified as epileptogenic (compromised) and 6 electrodes from regions that were classified as non-epileptogenic (non compromised). The selection of these electrodes was based, for each patient, on medical reports. The mean distance between electrodes was calculated and compared for each group of electrodes (epileptogenic vs non-epileptogenic) without finding statistical differences.

In our case we used Barret's scripts to calculate Φ_{AR}. A 200 samples (1 second) sliding window, with 100 samples

(500 ms) overlapping and τ = 50 samples (250ms) was used to generate the data matrices X employed to compute Φ_{AR}.

Finally, we computed $\Delta\Phi_{AR}$ computing the minimum Φ_{AR} inside a 1 second window taken right after the

seizure onset and subtracting a baseline value computed as the average of a 2.5 seconds window located 10 minutes before the seizure onset. We used the same approach to compute the signal power differences (ΔP) between pre ictal and ictal conditions.

It has been shown that integrated information is maximized when a system is functionally integrated and specialized [9], [10]. A reduced level of integration or specialization leads to a reduced value of Φ_{AR}. To understand the observed Φ_{AR} changes in terms of changes in integration and specialization, we analyzed the interaction between pairs of electrodes. We constructed the matrix R, equal to the absolute value of the correlation matrix, computed on the same time windows as Φ_{AR}. For each one of these matrices, we computed graph theory measures over a weight undirected graph with adjacency matrix L = 1 − R. In these graphs, nodes (electrodes) were close if their signals were correlated. We computed two graph-theoretic measures: the mean shortest path length (MSP) and the modularity (Q). The MSP is obtained by finding the minimum distance between each pair of nodes and taking their average. Modularity is defined as the average weight within communities minus the expected average weight for a random graph of equal in-degree and out-degree. Community partitioning was performed with the spectral method of Leich *et al* [11]. Both measures were computed with the “Brain Connectivity Toolbox”[12].

3. Results

In this study we analyzed iEEG recordings from 6 epilepsy patients (2 temporal and 4 frontal), candidates to surgery. All the subjects underwent presurgical evaluation at Hospital El Cruce “Nestor Kirchner”, Florencio Varela, Argentina, between 2012 and 2017. The mean age was 30 ± 6.86 years-old, the mean age at first seizure was 12.5 ± 6.5 years-old and 5/6 were males. The number of implanted electrodes was between 39 and 54 per patient.

A typical case is shown in Fig. 1a and Fig. 1b, where 5 microelectrodes and 5 macroelectrodes were implanted in the right amygdala, hippocampus, and insula. iEEG recordings lasting ten seconds are displayed in Fig. 1c and Fig. 1d, showing the activity of a compromised electrode (capturing epileptogenic activity in red) and the activity of six non-compromised electrodes (in black). The signals in Fig. 1c and Fig. 1d come from different seizures of the same patient. The main difference between them is that the crisis in Fig. 1c is associated with a CSS value of 6 (indicating consciousness loss), while the crisis in Fig. 1d has a value of 0 (no consciousness loss). Figures 1e and Fig. 1f present the values of Φ_A computed over the group of non-compromised electrodes in Fig. 1c and Fig. 1d throughout the entire recording (see methods). Notably, ΦAR exhibits an abrupt and sustained descent at the time of seizure onset only in the crisis where a deep loss of consciousness was reported.

When this phenomenon was analyzed across all patients and their crises, we found a correlation between the magnitude of Φ_{AR} change ($\Delta\Phi_{AR}$) and the CSS index for both non-compromised and compromised electrodes (Figs. 2a and 2b, respectively). We next investigated whether the observed changes in $\Delta\Phi_{AR}$ could be attributed to changes in the signal power. Although some functional dependence can be observed as in other studies [13], it is not strong enough to conclude that the changes in signal power are solely responsible for the observed changes in $\Delta\Phi_{AR}$ (Fig. 2c).

Interestingly, we observed that despite the changes in Φ_{AR} being larger for compromised electrodes compared to non-compromised ones (Fig. 2d), the correlation between $\Delta\Phi_{AR}$ and CSS value for compromised regions was lower, as shown in Fig. 2b.

According to the integration information theory of consciousness, the consciousness level is high when brain regions integrate information without losing their specialized functions. We therefore sought to explain the observed relationship between Φ_{AR} and CSS in terms of the observed integration and specialization in compromised and non-compromised electrodes. To this end we first computed matrix R, the absolute correlation matrix between pairs of electrodes (one matrix for compromised, and one for non-compromised electrodes, for each time window). We show in Fig. 3a the Φ_{AR} measured in one non-compromised electrode during a seizure, together with matrix R before (Fig. 3b) and during (Fig. 3c) the seizure. Then, for each matrix R we obtained matrix L = 1 - R, which we employed to define an undirected weighted graph. Each node in this graph stands for an electrode, and pairs of nodes are separated by a distance which is inversely proportional to their absolute correlation. We computed two graph-theoretical measures over this graph: mean shortest path, which quantifies the degree of coupling among recorded areas (a measure of integration), and modularity, which quantifies to what degree the graph can be clustered into groups of nodes characterized by being close to each other, and far from the others (a measure of specialization). Here, a lower mean shortest path is expected for high integration, and a low modularity is expected for low specialization.

We observed a decrease in both mean shortest path and modularity after seizure onset (Fig. 4a and 4b), pointing to an excess of integration together with a loss of specialization during the seizure. Compromised and non-compromised electrodes showed a qualitative similar picture, but differences appear when associated CSS values are taken into account (Fig. 4c and 4d). The drop in mean shortest path in compromised electrodes was significantly higher in seizures with profound loss of consciousness, in relation to seizures with moderate loss of consciousness, while modularity showed no significant changes (Fig. 4c). Conversely, non compromised electrodes showed the opposite behavior: no significant differences in mean shortest path, and a higher drop in modularity during seizures with profound loss of consciousness (Fig. 4d). These results show that the link between consciousness level and changes in Φ_{AR} can be explained in terms of an increment in integration in parallel with a loss in specialization during the epileptic crisis. Moreover, they point towards integration as the critical factor behind the higher variance explained by non-compromised electrodes in the relationship between Φ_{AR} and CSS (Fig. 2a and 2b)

4. Discussion

Consciousness is a fundamental characteristic of human experience and is closely linked to our ability to perceive, think, reason, and have subjective experiences. It has been studied for centuries by philosophers, scientists, physicians, among others, due to its relevance in understanding human behavior, self-perception, and mental disorders. In this paper, we had a unique opportunity to study it by accessing intracranial EEG (iEEG) records and investigate consciousness transitions in brain regions affected by acute epilepsy crises and some other non-epileptogenic regions. For this we selected the Integrated Information Theory (IIT) proposed by Tononi in [2], [9]. It is based on the idea that consciousness is not simply an emergent property of information processing, but rather it is a property related to the integration of information within a system. In short, and at the fundamental level, consciousness is integrated information and, in his own words, “the integrated information is the amount of information generated by a complex of elements, above and beyond the information generated by its parts” [14].

After computing Φ_{AR} and its correlation with the CSS index, we observed that the $|\Delta\Phi_{AR}|$ index better explains the variance in the CSS index when the selected electrodes were not within the epileptogenic region, even though it is, on average, greater within the epileptogenic regions. To rule out the possibility that these results could be explained by differences in signal amplitude during the epileptic crisis, we calculated the differences in signal power (ΔP) and correlated it with the CSS value. We found that the correlation is low and not statistically significant. This indicates that the observed correlation between $|\Delta\Phi_{AR}|$ and the CSS value is not solely influenced by differences in signal amplitude during the epileptic crisis. These results are consistent with those presented by Dong et al. [4]. In their study, the authors calculated the Φ index using an EEG signals database obtained from patients who were sedated using different doses of two types of sedatives, resulting in varying levels of consciousness. Their findings indicated that the alpha band Φ tended to differentiate states of consciousness. Furthermore, they demonstrated that the Φ index value decreases as sedation becomes more profound. Similar results were found by Nemirovsky et al. [5] using fMRI records from 17 patients who were also sedated with different doses. They computed $\mu[\Phi max]$, a weighted average of the Φ index over the time-series of different networks. The authors showed that the index is sensitive to the different doses in the fronto-parietal network (FPN), a network that is associated with consciousness.

We found a drop in the mean shortest path in the compromised regions for cases with profound loss of consciousness. This suggests that higher drops in Φ_{AR} with respect to the baseline could be attributed to high integration processes occurring in those epileptogenic regions. In contrast, for regions outside the epileptogenic areas, we observed a drop in modularity, indicating a loss of specialization during profound loss of consciousness, which causes a decrease in the Φ_{AR} index. These findings suggest that, during the epileptic crisis, the level of specialization drops outside the epileptogenic region, and this in turn leads to lower integrated information and a concomitant loss of consciousness, as evidenced through the CSS values.

5. Conclusions

The objective of this study was to determine whether the Φ_{AR} index, as proposed by Barret, could effectively characterize distinct levels of consciousness. Our results, which are novel as they stem from iEEG signals, provide further support for the sensitivity of the index to shifts in consciousness. To enhance our explanatory capacity, we conclude that the inclusion of mean shortest path and modularity indices augments the outcomes derived from Φ_{AR}. This additional insight aids in comprehending the underlying sources of its fluctuations.

Declarations

Data availability: The data that support the findings of this study are available from “Hospital El Cruce”, Buenos Aires, Argentina, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request to Dr. Silvia Kochen (skochen@gmail.com) and with permission of “Hospital El Cruce”, Buenos Aires, Argentina

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Figures

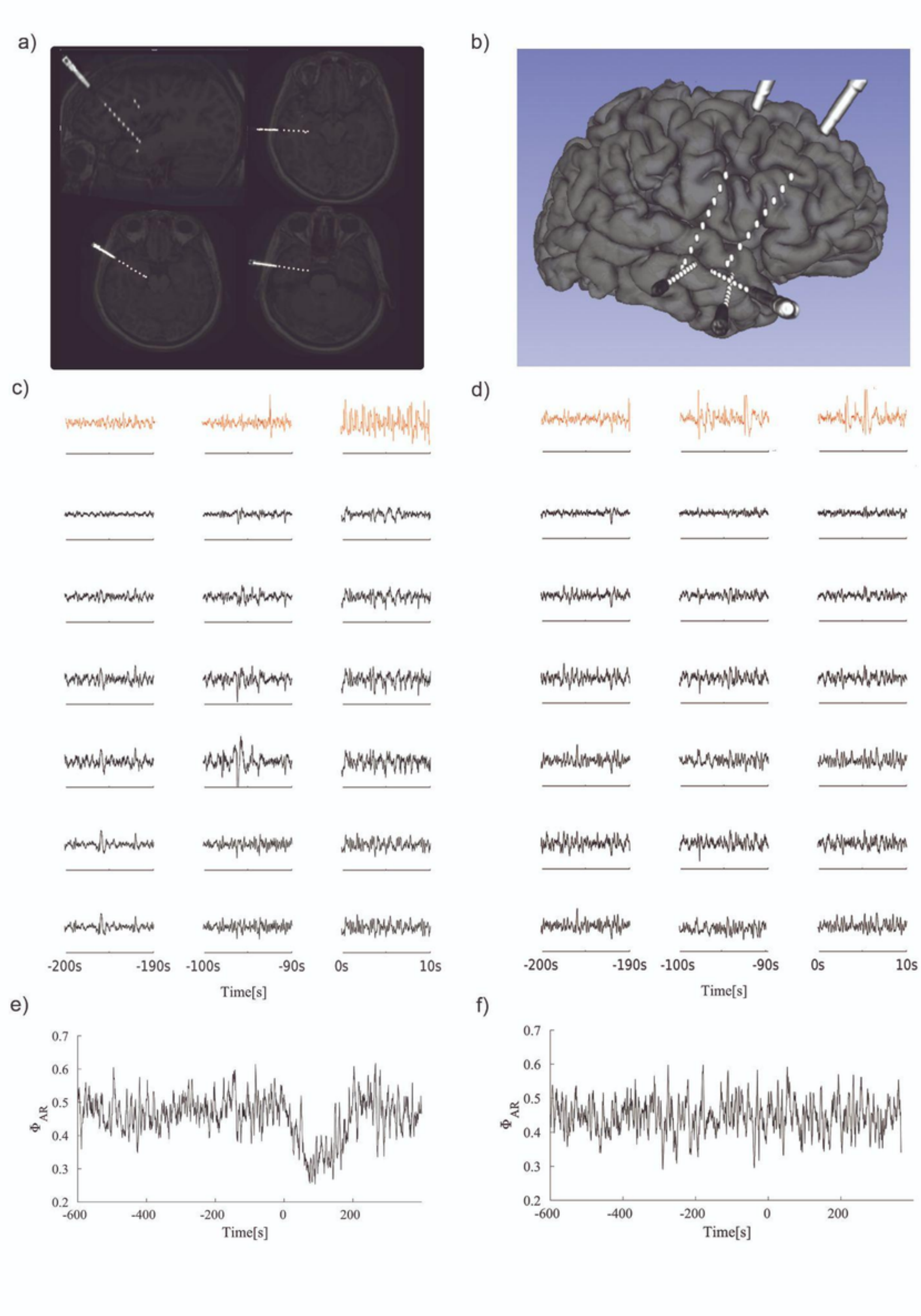

Figure 1

(a) Fusion of the pre-surgery magnetic resonance (MR) and post electrode implantation cerebral tomography (CT) image. **(b)** Post implantation three-dimensional brain reconstruction built from pre-implantation MR and post-implantation computed tomography (CT). **(c)** SEEG recording of one electrode in the compromised region (red) and six electrodes in the non-compromised region for a CSS value of 6. **(d)** SEEG recording of one electrode in the compromised zone (red) and six electrodes in the non compromised zone for a CSS value of 0. **(e)** Φ_{AR} value for the 6 SEEG non compromised region recordings in (c). (f) Φ_{AR} value for the 6 SEEG non compromised region recordings in (d).

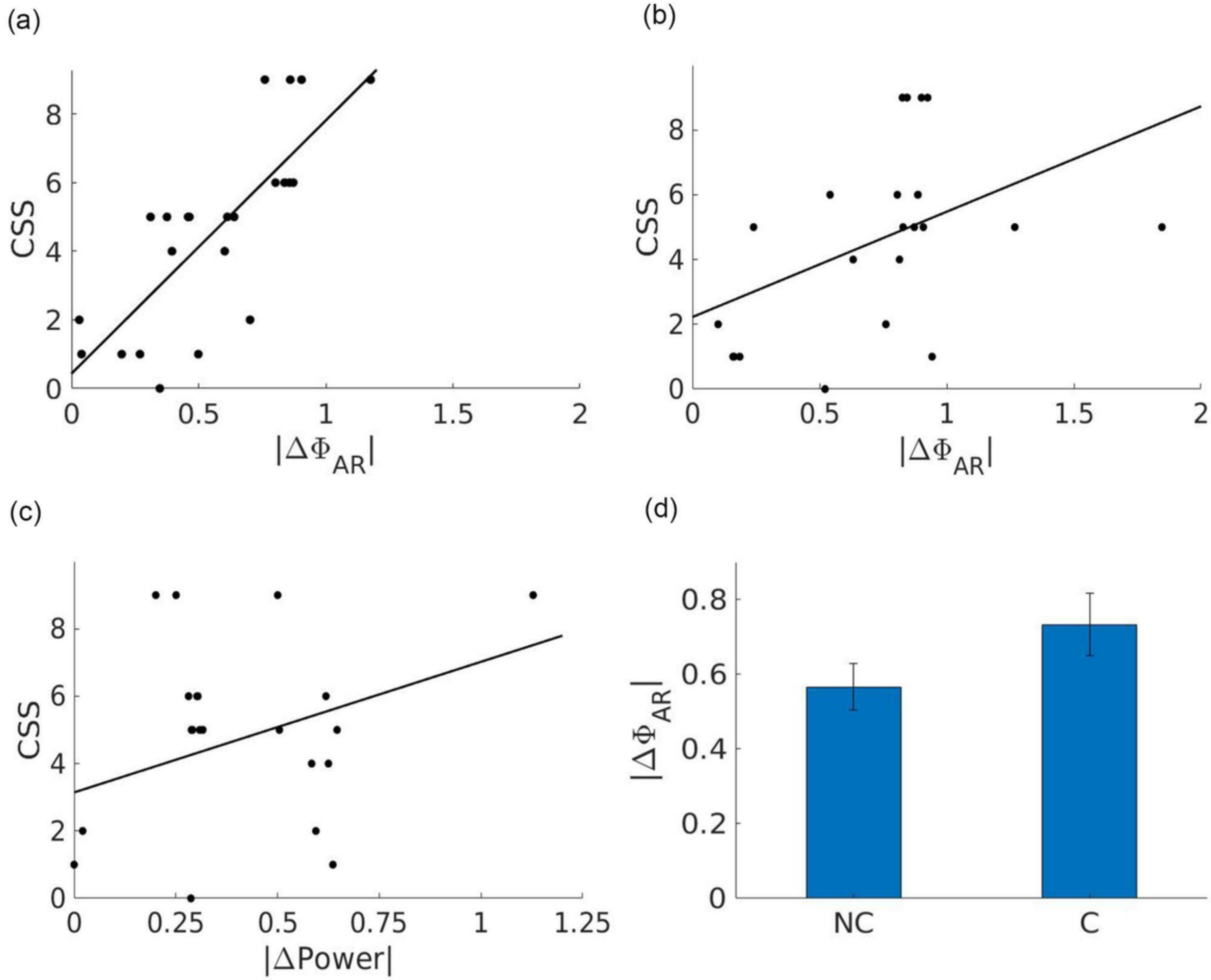

Figure 2

(a) Scatter plot of $|\Delta\Phi_{AR}|$ versus CSS for each recording in the non compromised regions. The Pearson correlation coefficient is 0.78 with p<5e-05 and linear fit equal to 7.38x - 0.43. **(b)** Scatter plot of $|\Delta\Phi_{AR}|$ versus CSS for each recording inside the compromised regions. The Pearson correlation coefficient is 0.4593, with p=0.0275 and linear fit equals to 3.25*x + 2.22, (c) Scatter plot of ΔPower versus CSS for each recording in the non compromised zone. The correlation value is 0.37 with p=0.08 and correlation function equal to 3.88*x + 3.14, (d) $|\Delta\Phi_{AR}|$ average value for compromised (0.73) and non compromised groups (0.57) comparison with p< 5e-09.

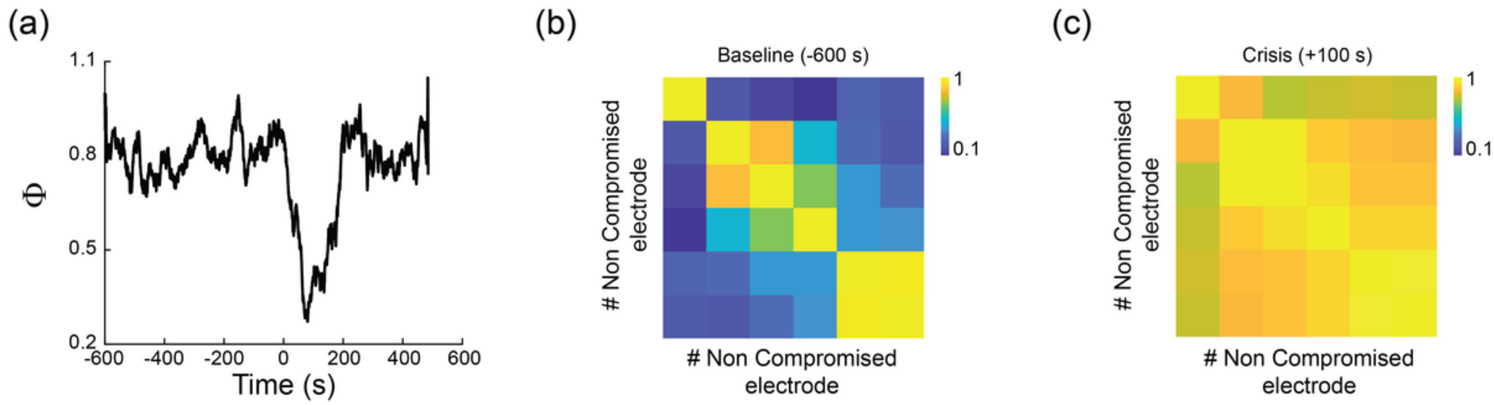

Figure 3

(a) Φ_{AR} value for a high CSS value non compromised zone record. **(b)** Electrodes correlation matrix for a 6 electrodes group during baseline(-600s). **(c)** Electrodes correlation matrix for a six-electrodes group 100 s after crisis.

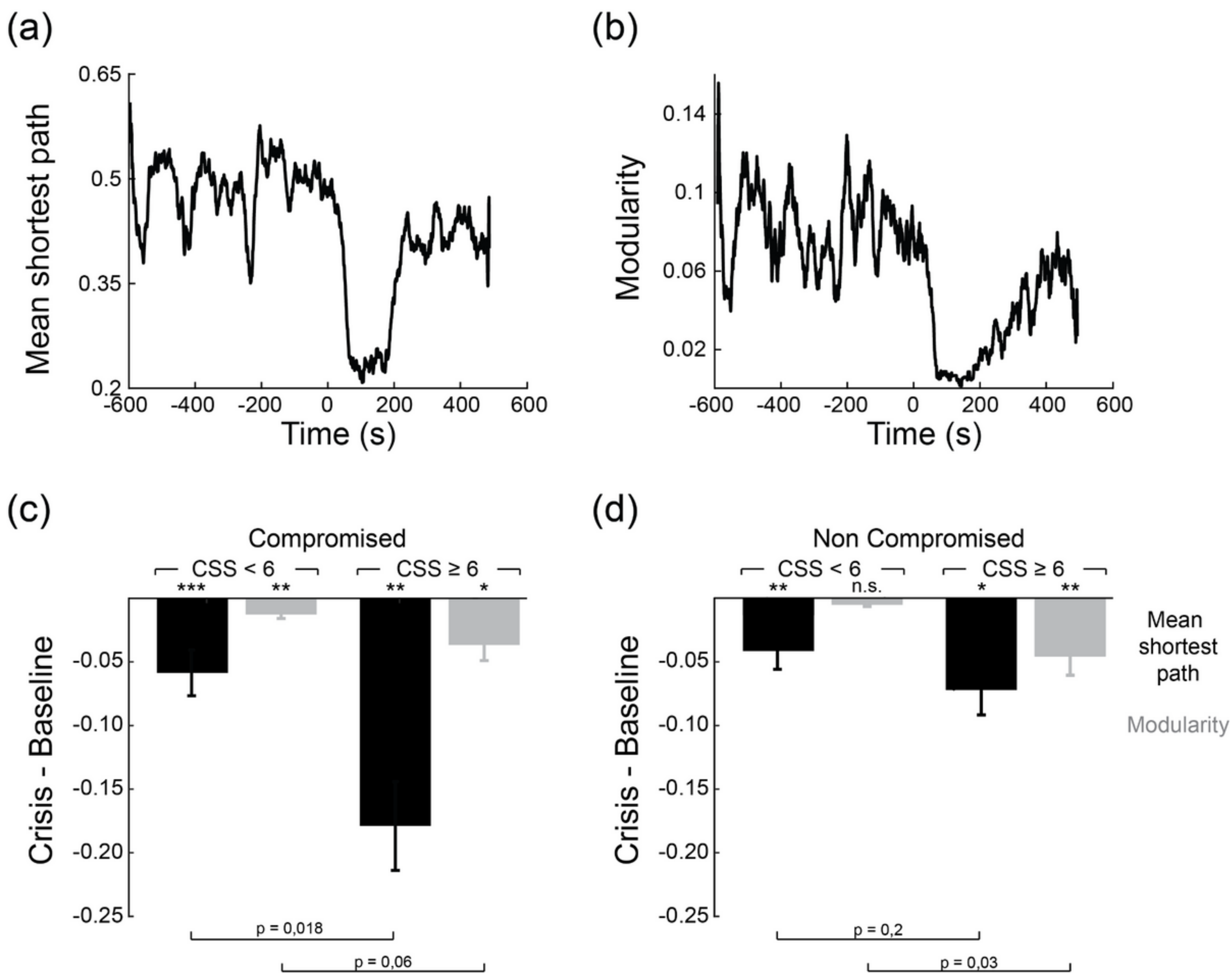

Figure 4

(a) Mean shortest path and **(b)** modularity index for the same case as in Figure 3. **(c)** Mean shorter path and modularity comparison when grouping by CSS<6 and CSS ≥6 for electrodes located in the compromised region. For the first case, the averaged mean shorter path value for the group is -0.059 ± 0.018 and modularity is -0.013 ± 0.003. For the second group the averaged mean shorter path value for the group is -0.18 ± 0.035 and modularity is -0.037 ± 0.012. **(d)**Mean shorter path and modularity comparison when grouping by CSS<6 and CSS ≥6 for electrodes located in the non compromised region. For the first case, the averaged mean shorter path value for the group is -0.042 ± 0.014 and modularity is -0.0053 ± 0.0013. For the second group the averaged mean shorter path value for the group is -0.072 ± 0.02 and modularity is -0.046 ± 0.015. (Crisis-basal significance with sign test (*: p<0.05, **: p<0.01, ***: p<0.001). Comparison between CSS groups with Wilcoxon rank-sum test).