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Research article

Enhanced gamma band mutual information is associated with impaired consciousness during temporal lobe seizures

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ABSTRACT

Background: Epileptic seizures are characterized by aberrant synchronization. We hypothesized that higher synchronization across the seizure onset zone (SOZ) channels during a temporal lobe seizure contributes to impaired consciousness.

New method: All symmetric bivariate synchronization measures were extended to multivariate measure by a principal component analysis (PCA) based technique. A novel nonparametric method has been proposed to test the statistical significance between increased synchronization across the seizure onset zone (SOZ) channels and reduced consciousness.

Results: Increased synchronization in the gamma band towards seizure termination significantly contributes to impaired consciousness ($p < 0.1$). Synchronization reaches its peak in the extratemporal region (frontal lobe) ahead of the temporal region ($p < 0.05$). Synchronization is prominent in beta and gamma bands by most methods and it is more in the second half of seizure duration than in the first ($p < 0.05$).

Conclusions: Mutual information is the only synchronization measure out of the six that we studied, whose increase can be associated with the loss of consciousness in a statistically significant way.

1. Introduction

Impaired consciousness in focal seizures is usually most profound late in the seizure and persists for up to several minutes after the termination of the seizure, during the post-ictal period (Blumenfeld and Taylor, 2003). The mechanisms of impaired consciousness during seizures are important to study as the most negative effects of epilepsy (including driving restriction, trauma, mortality and sudden unexpected death in epilepsy) are directly related to impaired consciousness. The neural underpinnings of impaired consciousness during seizures are variable and depend on epilepsy subtypes (focal or generalized epilepsy). Proposed mechanisms for focal seizures with impaired awareness (FSIA) (new nomenclature for complex partial seizures) includes network inhibition hypothesis (Yu and Blumenfeld, 2009; Englot et al., 2010), involvement of default mode network and altered thalamocortical synchronization within the global workspace of consciousness (Danielson et al., 2011; Bartolomei and Naccache, 2011; Lambert and Bartolomei, 2020). In this article we will continue to use the old terminology 'complex partial seizure' (CPS) for better readability.

Neuronal gamma band synchronization constitutes a fundamental process for all of cortical computations (Fries 2009). It is involved in modulating different aspects of consciousness (Ward, 2003), such as, visual awareness (Crick and Koch, 1990; Tallon-Baudry, 2009), face recognition (Rodriguez et al., 1999), associative learning (McIntosh et al., 1999), conscious perception (Melloni et al., 2007) and declarative memory formation (Fell et al., 2001). Conscious thinking is often aided by working memory storage and long-term memory retrieval. Both the processes may interact in the hippocampus (Fell and Axmacher, 2011). An increase in coherence of gamma and theta oscillations in the hippocampus, amygdala and neocortex was predictive of immediate recall performance in a verbal learning task (Babiloni et al., 2009). In general, conscious awareness may arise from synchronous neural oscillations occurring globally throughout the brain rather than from the locally synchronous oscillations that occur when a sensory area encodes a stimulus (Ward, 2003). Long distance cortico-cortical synchronization at beta and gamma frequencies has been implicated in consciousness (Dehaene and Changeux, 2011). It is possible that during epileptic seizures excessive synchronization in the form of a nonlinear correlation

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(Wendling et al., 2001) across all the frequency bands overloads the brain structures involved in conscious processing leading to impaired consciousness (Lambert et al., 2012; Arthuis et al., 2009).

Synchronization is a ubiquitous phenomenon in neuroscience. It is present from cellular level (Steinmetz et al., 2000) to systems level in primate brains (Ward, 2003). However, in neuroscience synchronization is a generic term, interpreted and measured differently in different contexts. Sometimes it is phase synchronization (Rodriguez et al., 1999), some other times it is cross correlation (Schindler et al., 2007) and yet other times it is nonlinear correlation (Lambert et al., 2012; Arthuis et al., 2009; Wendling et al., 2001), mutual information (MI) (Tononi, 2004; Mars et al., 1985), mean phase coherence (Mormann et al., 2000) or phase locking value (Aydore et al., 2013).

Study of synchronization through multiple measures across intracranial EEG (iEEG) channels in the temporal and extratemporal (mainly frontal lobe) region across delta, theta, alpha, beta and gamma bands before, during and after epileptic seizures vis-à-vis the state of consciousness of the patient may offer us important insights into the relationship between seizure and consciousness in different EEG bands, which has so far not been explored.

2. Methods

2.1. Patient selection and data acquisition

Of the 42 adults with drug-refractory focal epilepsy who have undergone intracranial EEG investigation to localize seizures at the University of Alabama at Birmingham, AL level - IV epilepsy center between 2014 and 2017, we have selected 11 patients for this study. The patient selection criteria were as following: a) seizure onset was within the mesial temporal lobe structures (amygdala, hippocampus, parahippocampal gyrus, temporal pole); b) have undergone anterior temporal lobectomy; c) had at least six months post-resection follow up, and d) seizure outcome was favorable (Engel I and II) (Engel et al., 1993). The rationale for selecting patients with good surgical outcome was to have confirmation of the seizure onset zone (SOZ).

All patients had undergone standard investigation before intracranial EEG study, and this includes 3T MRI of the brain, 18-fluorodeoxyglucose PET scan, Magnetoencephalography, and scalp EEG investigation. Out of the eleven patients recruited in the study, ten had robot-assisted stereo EEG investigation. Depth electrodes (PME electrodes, 1.4 mm contacts) were implanted targeting the anterior and posterior hippocampus, amygdala, temporal pole, superior temporal gyrus, orbitofrontal, lateral prefrontal, anterior insula, anterior cingulate and parahippocampal gyrus. In one subject (subject 4), grids, strips, and a depth electrode were placed for electrocorticography targeting the hippocampus, subtemporal, orbitofrontal, and lateral temporal regions. Video EEG was sampled using Natus Xltek EEG machine at sample frequencies mentioned in Table 1. All video EEG and other investigations were discussed in a multidisciplinary epilepsy surgical conference to confirm the onset of seizures and seizure onset channels. These are standard procedures followed at any level – IV epilepsy center. Written consent was obtained before implantation. The IRB approved the retrospective analysis of data.

2.2. Selection of EEG channels

To avoid increased computation of all the recorded channels, we focussed our analysis on selected channels that were labeled as a) SOZ and b) LIC- least involved channels. SOZ channels are located in the temporal region, and LICs are in the extratemporal region. We have selected these channels by visual and quantitative analysis of EEG in a systematic way, as described below.

Initially, we calculated the epileptogenicity index (EI) of all the recording channels. The EI score of a channel is a measure of

Table 1. Summary of patient demographics and seizures.

Subject	Seizure	Age	Gender	SOZ Channels	Pre seizure vigilance	Seizure	Treatment	Outcome
1	1	23	F	Left Hpc, PHG	Awake	SP	Left ATL	I at 9 mo
	2			Left Hpc, PHG	Awake	CP		
2	3	19	M	Right Amyg Hpc	Awake	CP	Right ATL	I at 22 mo
	4			Right Amyg Hpc	Awake	CP		
	5			Right Amyg Hpc	Awake	CP		
3	6	38	M	Right Hpc, PHG	Sleep	sGTC	Right ATL	II at 14 mo
	7			Right Hpc, PHG	Awake	CP		
4	8	21	F	Left PHG, STG, MTG,	sleep	sGTC	Left ATL extended to lateral temporal	I at 12 mo
	9			Left PHG, STG, MTG	sleep	CP		
	10			Left PHG, STG, basal temp	Awake	CP		
5	11	25	F	Left Amyg, Hpc, Tp	Awake	CP	Left ATL	I at 16 mo
	12			Left Amyg, Hpc, Tp	Awake	sGTC		
6	13	42	M	Right Hpc, PHG, basal temp	Awake	sGTC	Right ATL	II at 14 mo
	14			Right Hpc, PHG, basal temp	Awake	sGTC		
7	15	24	F	Left mesial temp remnant	Awake	CP	Left residual mesial structures	II at 17 mo
	16			Left mesial temp remnant	Awake	CP		
8	17	44	M	Right Hpc, PHG, basal temp	sleep	sGTC	Right ATL	I at 18 mo
	18			Right PHG, basal temp,	Stg II sleep	sGTC		
9	19	37	M	Left Hpc, PHG, basal temp	Awake	CP	Left ATL	I at 20 mo
	20			Left Hpc, PHG, basal temp	Awake	CP		
10	21	22	M	Left Hpc, Amyg	Awake	CP	Left ATL	I at 14 mo
	22			Left Hpc, Amyg	Awake	CP		
11	23	19	M	Right Hpc, Amyg	Awake	CP	Right ATL	I at 16 mo

Note: Sample frequency is 2048 Hz except for seizures 11, 12 (2000 Hz each) and 19, 20 (1000 Hz each). Hpc = Hippocampus, PHG = Parahippocampal gyrus, Amyg = Amygdala, STG = Superior temporal gyrus, MTG = Medial temporal gyrus, Tp = Temporal pole, ATL = Anterior temporal lobectomy, SP = Simple partial seizure (new classification focal seizure with awareness), CP = complex partial (new classification focal seizure with impaired awareness), sGTC = secondary generalized tonic-clonic (new classification focal to bilateral tonic-clonic); SOZ = seizure onset zone.

epileptogenicity of the brain region covered by the channel. For detail, please see (Bartolomei et al., 2008). Channels with EI > 0.2 are considered within the SOZ. Channels with score <0.2 were all eligible for potential least involved channels. To select the LIC channels, we first identified seizure termination and then visually inspected EEG from all recorded channels moving backward towards seizure onset. For focal seizures without generalization, we have selected LICs that had no ictal epileptiform activity on visual inspection. For focal seizures that were generalized, we selected LICs that had late (or last) propagation of ictal epileptiform activity.

2.3. Selection of seizures and scoring of consciousness

23 seizures in 11 patients have been studied. Detail of the patients and the seizures have been furnished in Table 1. Selection criteria for seizures were as follows - a) only spontaneous seizures were selected; b) video of the seizure was available; c) electrographic seizures that lacked any clinical accompaniment were excluded; d) nursing staff was able to examine the patient during and after the seizure. In our epilepsy center, we have adopted a protocol to examine the patient during and after seizure by the nursing staff. The examination includes: a) evaluating awareness by interaction with the patient (asking name, place, date); b) visual attention by showing sign or gesture, if they follow them or an object (such as, pen), during the conversation; c) motor examination by asking them to lift arms, legs d) speech/language by asking them to read a signboard and e) asking the patient to report what they felt during a seizure. These examinations were continued in the postictal period and, at times, continued periodically till the patient was back to baseline. By reviewing the video, one of the authors (SP) scored consciousness towards the termination of seizure. This scale takes into account different aspects of consciousness in humans: (i) unresponsiveness (Criteria 1 and 2); (ii) visual attention (Criterion 3); (iii) consciousness of the seizure (Criterion 4); (iv) adapted behavior (Criterion 5); and (v) amnesia (Criteria 6 and 7) (Arthuis et al., 2009).

2.4. Bivariate measures to analyze synchronization

Measures like correlation, coherence, phase synchronization, phase-locking value, nonlinear correlation or h^2 and mutual information are widely used to estimate the interdependence between two signals. Mutual information calculates this interdependence in terms of an information distance measure, called Kullback-Leibler divergence (Cover and Thomas, 2006) from the joint distribution of the two random variables (signals) to the product of the marginal distributions. Mutual information $I(x,y)$ between two-time domain signals x and y is given by

$$I(x,y) = \sum_x \sum_y p(x,y) \log \frac{p(x,y)}{p(x)p(y)}, \tag{1}$$

for discrete time signals x and y. Clearly, when x,y are independent $I(x,y) = 0$, and $I(x,y) > 0$ otherwise. The most challenging part of implementation of (1) is estimating $p(x,y)$, which has been tackled by introducing a motif based measure (Lin et al., 2002) described below.

It has been mathematically proved that information is encoded in a time series in terms of three point motifs or 3-motifs (Majumdar, 2018; Majumdar and Jayachandran, 2018). Even prior to this theoretical result, 3-motifs generated by permutation of the 3 values, were utilized to extract information out of EEG signals (Olofsen et al., 2008). Those $3! = 6$

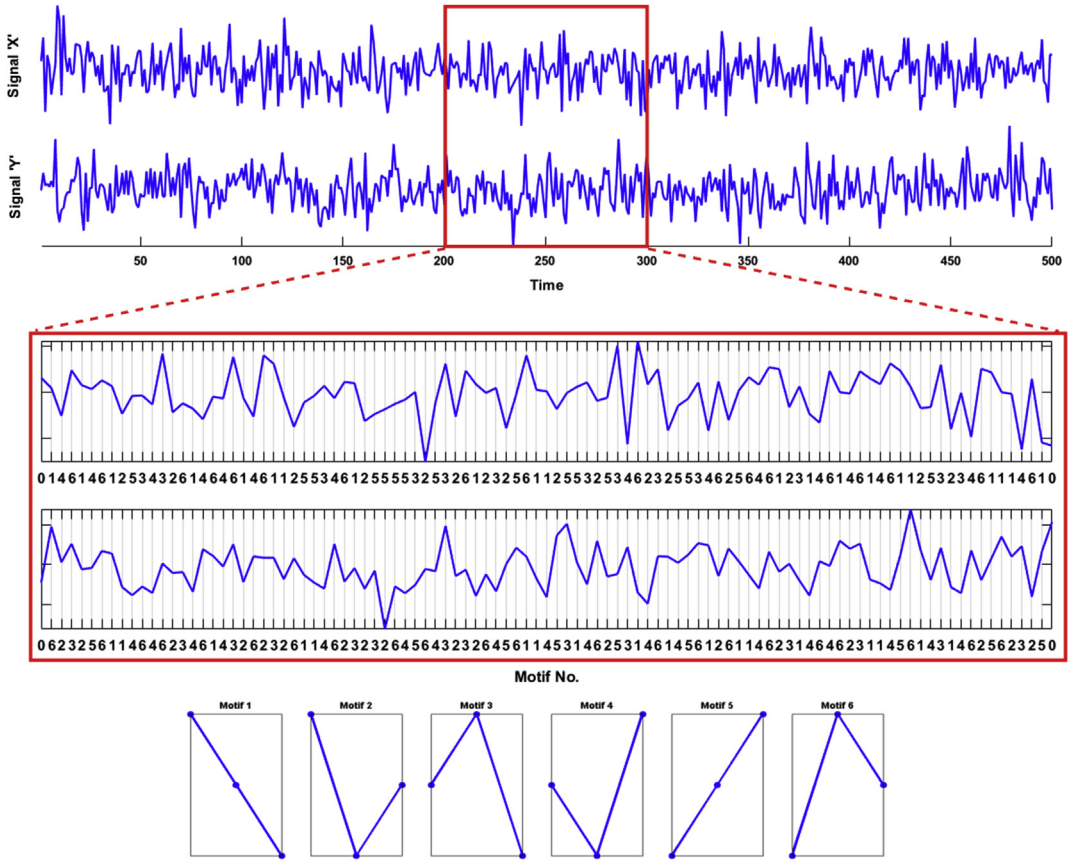

Figure 1. Permutation 3-motif decomposition of discrete signals X and Y (first two plots in the top). Signal motif matrix in the middle (within the red rectangle), which is a magnified window of the signal pair in top, and all 6 3-motifs are numbered at the bottom. These are the same motifs as in (Olofsen et al., 2008) and (Li and Ouyang, 2010).

motifs (Figure 2) have been utilized to measure Permutation Conditional Mutual Information (PCMI) between two signals (Li and Ouyang, 2010). PCMI gives a directional measure of how one signal is dependent on the other.

Here we have utilized the same 3-motifs to measure MI between two discrete signals (Figure 1). Since there are 6 number of 3-motifs altogether let us number them from 1 to 6. Take a window of length, say 1000 samples in both the signals x and y, starting and ending at the same time across the signals. There are a total of 998 3-motifs in the window from each of the signals. Say, the first motif in x is the motif number 1 and the first motif in y is the motif number 6 (Figure 1).

Then in the 2×998 signal motif matrix the first column will be $\begin{bmatrix}1\\6\end{bmatrix}$. The frequency density of $\begin{bmatrix}1\\6\end{bmatrix}$ over the 998 motif window will be $p(1,6)$. Similarly, if we consider the frequency density of all the columns of the signal motif matrix, we will eventually get a frequency estimate of $p(x,y)$ and will be able to estimate $I(x,y)$ from (1). $p(x), p(y)$ and $p(x,y)$ are shown in Figure 2.

2.5. Multivariate methods to analyze synchronization

For extension of the synchronization measures from two signals to more than two signals we have used the procedure of Schindler et al. (2007). In Schindler et al., 2007 the extension was done to generalize the correlation measure between two epileptic iEEG signals to more than two epileptic iEEG signals during seizures. Since here our purpose is the same, we have chosen this extension procedure to generalize synchronization measures between two signals to more than two signals. If there are n number of iEEG channels we form the $n \times n$ matrix, whose ijth entry is $I(x_i, y_j)$ over a window, where x_i is the iEEG signal collected from the ith channel. This matrix is a symmetric matrix and therefore all eigen values are real (for nonlinear correlation or h^2 measure we have taken $a_{ij} = \frac{a_{ij}+a_{ji}}{2} = a_{ji}$, where a_{ij} is the ijth entry of the matrix). By sliding the window we take only the highest eigen value from each of the windows. The plot of the highest eigen value over the time windows will give the ensemble synchronization across all the n channels (Schindler et al., 2007).

2.6. Nonlinear nonparametric association measure

In order to establish an association between the level of synchronization across the SOZ channels (Table 2) and the consciousness score (Table 3) we have devised a novel nonlinear nonparametric statistical measure (for detail see (Majumdar and Dheer 2018)). The hypothesis to be tested here is "Higher synchronization across the SOZ channels during the latter part of the temporal lobe seizure leads to impaired consciousness (i.e., higher consciousness score)." We treat synchronization measure by a particular method as the independent variable and consciousness score as the dependent variable. First, take the median value of synchronization across SOZ channels during the second half of the seizure. Increasingly order those values (all values are different for the simplest case, which is sufficient for the current work, see Majumdar and Dheer 2018 for how to resolve a tie). Plot the synchronization (abscissa) versus consciousness score (ordinate) graph. This is the plot of the consciousness score as the function of synchronization. From such plots, it will be clear that the association between synchronization and consciousness score (the higher the score, the more is the loss of consciousness (Arthuis et al., 2009)) is not linear and therefore cross-correlation or Pearson's correlation cannot be an appropriate measure of the relationship between them. A different measure is needed, which must be a nonlinear measure.

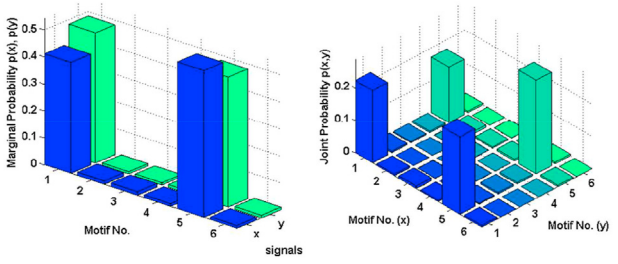

Figure 2. On the left, $p(x)$ as frequency density of 6 3-motifs in $s(t)$ has been shown in blue histogram and the same for $a \le t \le b$ as $p(y)$ has been shown in green histogram. On the right, the joint probability density function $p(x,y)$ has been plotted.

If increasing synchronization produces increasing consciousness score (i.e., enhanced synchronization impairing consciousness), the difference operation on the consciousness score as a function of synchronization value should produce only positive values. Let there are $n+1$ number of synchronization values and consciousness scores associated with $n+1$ number of seizures. After the first difference operation on the consciousness scores with respect to the synchronization values there will be only n number of values. Negative values will indicate with increasing synchronization consciousness score is decreasing, i.e., consciousness is impaired less, which is the null hypothesis. What is the probability that this null hypothesis will be true? If we assume negative and nonnegative sign of the difference operation is equally likely we can take the probability of each to be 0.5. If there are $r \le n$ number of negative values among n difference values, the cumulative probability $p(H_0)$ of the null hypothesis H_0 to be true is

$$p(H_0) = \sum_{k=1}^{r} \frac{n!}{k!(n-k)!} \frac{1}{2^k} \frac{1}{2^{n-k}} = \sum_{k=1}^{r} \frac{n!}{2^n k!(n-k)!} = \frac{n!}{2^n} \sum_{k=1}^{r} \frac{1}{k!(n-k)!} \quad (2)$$

which means up to $r \le n$ number of negative difference values may occur. (2) is valid because, for $k \le r$, if there are exactly k number of negative difference values out of n number of difference values, there will be exactly $n-k$ number of nonnegative difference values. This is a typical case of binomial density with probability $\frac{n!}{k!(n-k)!} \frac{1}{2^k} \frac{1}{2^{n-k}}$. When there are r number of negative difference values we take the cumulative probability of occurrence of up to r number of negative values, which is given by (2). If the value of $p(H_0)$ becomes < 0.1 (i.e., the chance of the null hypothesis to be true is less than 0.1), we can reject the null hypothesis. Subsequently, the alternative hypothesis, "Higher synchronization across the SOZ channels during the seizure leads to impaired consciousness (i.e., higher consciousness score)," may be accepted with $p < 0.1$.

3. Results

3.1. Patient demographics

Twenty-three seizures from 11 patients have been studied. Detail of the patients, seizures, and treatment outcomes (Engel classification) have been furnished in Table 1. Seven seizures were secondarily generalized, while 15 were complex partial seizures. Seizure duration and the highest consciousness score during the seizure is tabulated in Table 3. Consciousness was impaired if the consciousness score was greater than 2.

3.2. Comparison of various measures of synchronization

In Figure 3 we have presented a comparison among various synchronization measures prevalent in Neuroscience. Since synchronization has been studied most extensively during epileptic seizures, we have presented our results using different synchronization measuring algorithms on a pair of human iEEG signals (unfiltered) collected before, during, and after an epileptic seizure. (See Fig. S1, Fig. S2, and Fig. S3 in the Supplementary material for generalization of those measures to more than two signals). All computations in this paper have been done with a

Table 2. Comparison of median values between two halves of 23 seizure durations by different synchronization measures.

	Amplitude correlation	Coherence	Mutual information	Phase locking value	Phase synchronization	Nonlinear correlation (h^2)
Delta	0.3656	0.1172	0.1362	0.3005	*0.0522*	0.6994
Theta	0.1362	0.9808	*0.0631*	*0.08*	0.2137	0.2601
Alpha	**0.0097****	0.1882	0.1572	0.2799	0.311	**0.0067****
Beta	**0.0024****	0.6001	**0.0349***	*0.0522*	0.205	**0.0207***
Gamma	**0.0007****	**0.0458**	**0.0037****	0.1172	**0.003****	**0.0015****

Note: Bold indicates median ensemble synchronization across the onset zone channels during second half of seizure is greater than that of the first with ** is for $p < 0.01$ and * is for $p < 0.05$. The italic indicates the same holds with $p < 0.1$.

1-second non-overlapping window. Varying window length didn't alter the trend of synchronization.

Synchronization during a seizure is a complex, heterogeneous process over time and space (Jiruska et al., 2013), which has been captured by the methods in Figure 3. However, synchronization is the highest towards the end of seizure which may lead to spontaneous termination (Majumdar et al., 2014), which is also clear from Figure 3. Note that MI lies within a smaller range compared to all other measures in Figure 3 and also it is relatively less jittery among the methods studied.

3.3. Changes in synchronization with seizure progression

There is a progressive increase in synchronization toward seizure termination and in postictal period for all the measures of synchronization (Figure 3). As CPSs progress from onset to termination, there is an increase in synchronization in beta and gamma frequency bands (particularly in gamma), across all SOZ channels (the most involved channels) (Table 2). Each bivariate measure has been extended to a multivariate measure. Each of the 23 seizure durations has been divided into two halves. Then the median value of each measure from each half has been compared with that of the other half by Wilcoxon signed-rank test (left tail test with $p < 0.01$ and $p < 0.05$). The null hypothesis is median of the first half $\geq$ that of the second and the alternative hypothesis is median of the first half $<$ that of the second. The values have been derived for each frequency band and by a synchronization measure, as shown in Table 2 and Figure 4. Statistically significant values have been shaded in Table 2. Median of the second half $>$ median of the first half in the gamma band by all measures except the phase-locking value (PLV). Median of the second half $>$ median of the first half in the beta band by all measures except the coherence and (Hilbert) phase synchronization. Dominant synchronization in the second half is least significant in the delta band and only moderately significant in the theta band. The same trend in alpha band is highly significant only according to cross-correlation and nonlinear correlation (h^2), but quite insignificant according to coherence, mutual information, phase locking value and phase synchronization (Table 2 and Figure 4).

We can conclude that synchronization across methods is higher in the second half of the seizure duration than in the first based on boxplot of Figure 4. From Figure 4 it is clear that beta-band synchronization by the studied methods is more subdued than the trend in the gamma band. Even after the seizure offset, synchronization remained higher for several seconds in these two bands in SOZ channels across the methods.

We have extended the pairwise analysis of synchronization to a higher dimension following Schindler et al. (2007). However, if we are to measure synchronization across all the 150 to 240 channels, we will have to calculate $n \times n$ matrix multiplication for $150 \leq n \leq 240$, for each time window across the n iEEG signals. The computation becomes so huge that for little more than 100 channels a dual Xeon E5-2620v3 processor-based GPU workstation (with Nvidia K40 Tesla card) with 256 GB RAM ran out of memory midway through the computation (executed through MATLAB). So, we kept our analysis confined within the most involved channels (the SOZ channels) and the least involved channels (Figure 5) in each seizure. We also randomly added other channels in the above two sets, but the trend didn't change. From this, we conclude that synchronization remained high across the channels towards the offset of the seizures, particularly in the higher frequency bands implicated in higher cognitive functions and consciousness.

3.4. Associating seizure with loss of consciousness

In order to establish an association between the level of synchronization across the SOZ channels (Table 2) and the consciousness score (Table 3) we are to invoke formula (2). It is assumed the more is the synchronization, the more severe is the seizure. Our hypothesis is, "higher synchronization across the SOZ channels during the latter part of the seizure leads to impaired consciousness (i.e., higher consciousness score)." We treat synchronization by a particular method as the independent variable and consciousness score as the dependent variable. First, take the median value of synchronization across SOZ channels during the second half of the seizure. For a particular synchronization measure, there will be 23–1 = 22 such values (the first

Table 3. Seizure duration and total consciousness score during the second half of the seizure.

Sz No.	Sz duration in sec (#SOZ channels, #LIC)	Consciousness Score
1	280 (12, 31)	0
2	182 (12, 31)	3
3	180 (6, 12)	3
4	173 (6, 12)	1
5	77 (6, 12)	2
6	71 (7, 6)	4
7	182 (7, 6)	4
8	167 (10, 12)	6
9	75 (10, 12)	2
10	51 (10, 12)	8
11	89 (12, 16)	7
12	119 (12, 16)	9
13	52 (10, 5)	4
14	90 (10, 5)	9
15	134 (12, 14)	1
16	100 (12, 14)	5
17	83 (6, 6)	8
18	88 (6, 6)	7
19	67 (5, 7)	4
20	63 (5, 7)	6
21	155 (11, 26)	6
22	131 (11, 26)	4
23	147 (8, 6)	4

Note: Total number of implanted channels per patient varies from 150 to 240. SOZ = seizure onset zone, LIC = least involved channels.

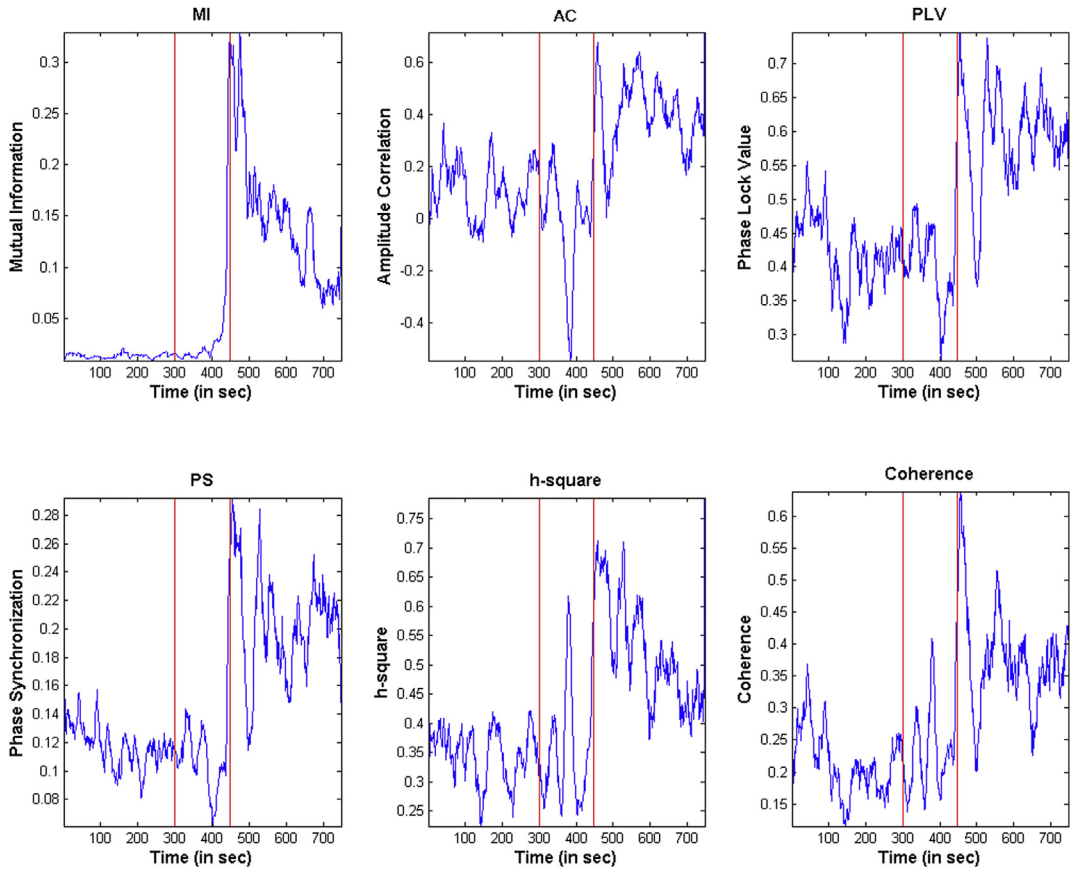

Figure 3. Comparison among Mutual Information (MI), Amplitude Correlation (AC), Phase Locking Value (PLV) (Aydore et al., 2013), (Hilbert transformation based) Phase Synchronization (PS) (Tass et al., 1998), Nonlinear Correlation or h-square value (Wendling et al., 2001) and coherence (Bastos and Schoffelen 2016) over a pair of pre-ictal, ictal and postictal signals. Vertical lines indicate seizure onset and offset time points.

seizure is simple partial with 0 consciousness score), one for each seizure. Increasingly order those values (all synchronization values are different for each synchronization measure, see (Majumdar and Dheer 2018) for how to resolve a tie). In Figure 6 synchronizations (abscissa) versus consciousness score (ordinate) graph has been plotted. From Figure 6 it is clear that the association between synchronization and consciousness score is not linear, and therefore cross-correlation cannot be an appropriate measure of the relationship between them. In formula (2) the values we have used are $n = 22 - 1 = 21$ and $r = 7$ (as there are 7 decreasing trends of consciousness score with respect to the increasing synchronization values clearly visible in Figure 6).

In Table 4 the statistical significance values of the effect of synchronization across the SOZ channels during the second half of the seizure on impairment of consciousness by the 6 synchronization measures at beta and gamma range have been furnished. It is clear from Table 4 that if we relax the p-value to $p < 0.1$ from the more prevalent $p < 0.05$ only, then the mutual information measure of enhanced synchronization across the SOZ channels during the second half of the seizure leads to impaired consciousness. It is clear from Table 4 that no other synchronization measure achieved the level of statistical significance value necessary to accept the hypothesis, "Higher synchronization across the SOZ channels during the latter part of the temporal lobe seizures leads to impaired consciousness."

We have also analyzed the LIC, which was localized to extratemporal lobe regions. Figure 5 presents a snapshot of LICs during a seizure. In the gamma range, the maximum synchronization value across the LICs during a seizure by mutual information and phase synchronization occurred ahead of the maximum synchronization value across the SOZ channels ($p < 0.05$ by Wilcoxon signed-rank, right-tailed test). The results have been summarized in Table 5 (also see the Supplementary material, in which mutual information plots across SOZ channels as well as the LICs for the seizures Sz1 through Sz23 have been presented in each band from pre-ictal through ictal to postictal period).

Summarizing the above results, we can conclude the following: 1) Synchronization is the highest in gamma band (according to phase synchronization and mutual information measures of synchronization) during CPS in patients with TLE (Table 5). 2) Synchronization is higher across the SOZ channels in the second half of the seizure compared to the first half (Table 2 and Figure 4, also see the Supplementary material). 3) Synchronization during seizure reaches its peak values across the extra-temporal (mainly frontal lobe in our study) LICs ahead of the peak synchronization value across the SOZ channels (Table 5). Synchronization was highest in the gamma band (30–80 Hz).

4. Discussion

4.1. Consciousness score

In this study we have investigated if loss of consciousness (LOC) during a seizure is related to altered synchronization within temporal lobe and extra-temporal lobe regions. As in the previous study (Arthuis et al., 2009), where patient's consciousness score was measured during seizure, we also measured the scores for consciousness during the seizure. This score was originally proposed in (Arthuis et al., 2009) and a score of 3 or more means impaired consciousness. In Arthuis et al., 2009 distinction has been made between moderate and severe loss of consciousness. But we only made distinction between intact consciousness and impaired consciousness, which we also referred to as

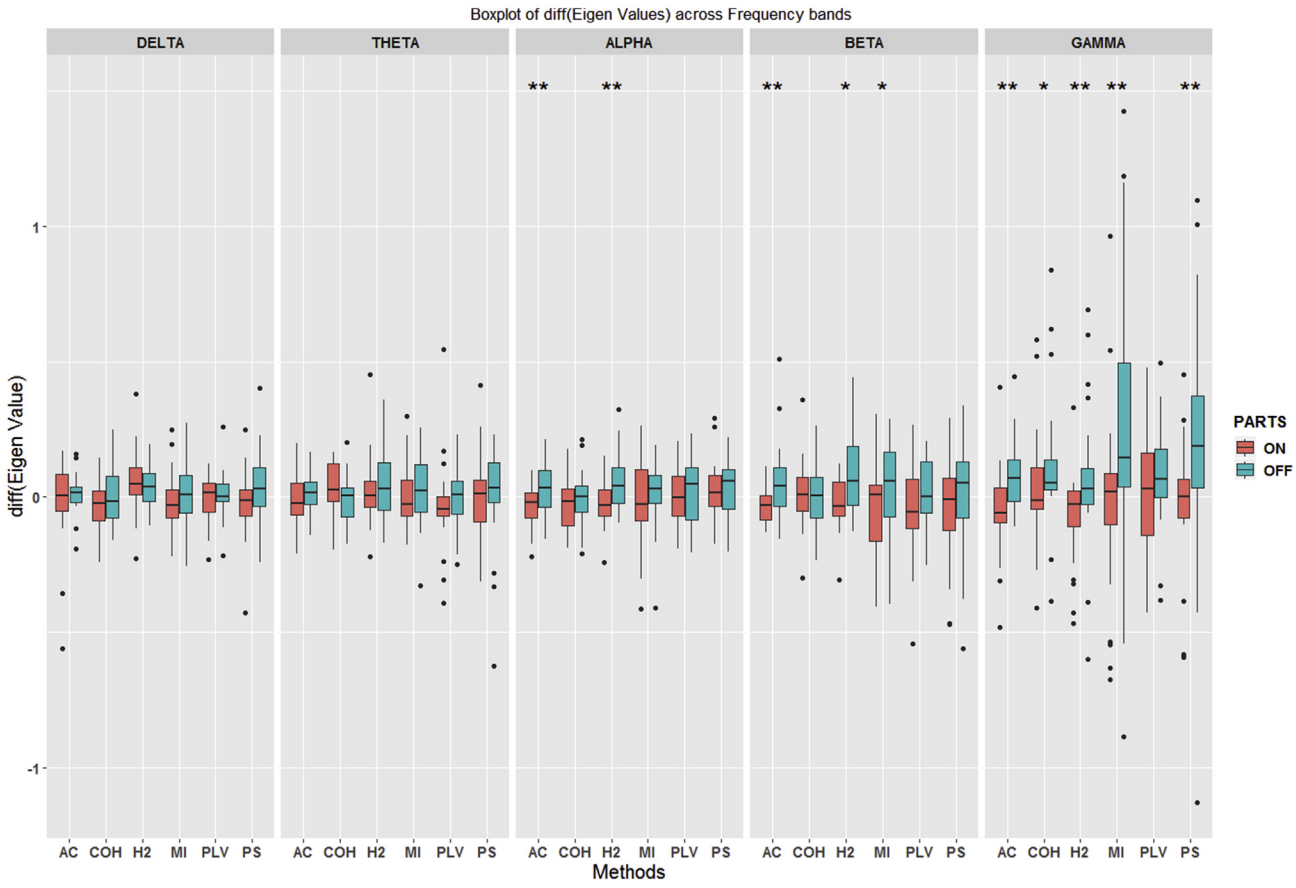

Figure 4. Box-plot of comparison (by Wilcoxon signed rank test) of median value of first difference of synchronization values across SOZ channels at different frequency bands by different methods. Median values of the first half and of the second half of the seizure duration have been compared. Red and blue box correspond to the first and the second half of the seizure duration respectively. Abbreviation of synchronization measures are appearing at the bottom. ** is for $p < 0.01$ and * is for $p < 0.05$.

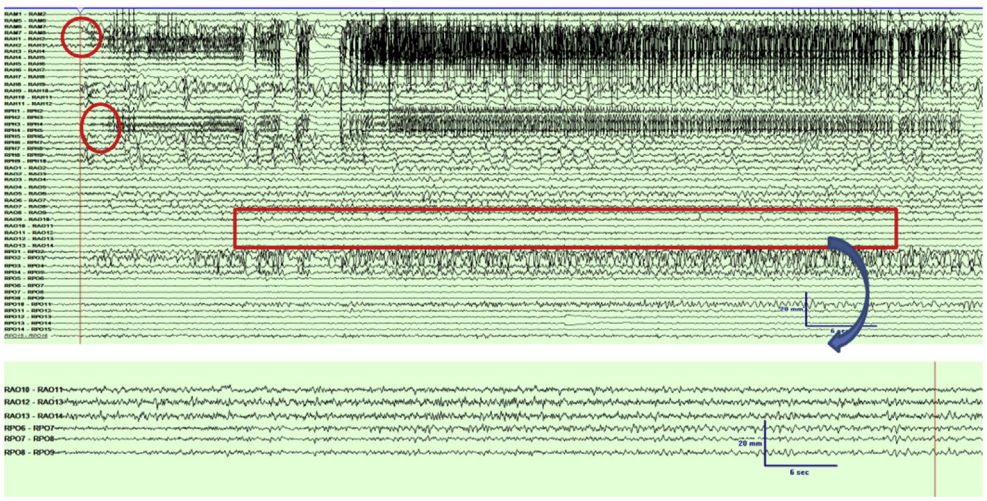

Figure 5. Electrical activities in the SOZ channels and in the least involved channels (located in the extratemporal region, which is mainly frontal lobe in our study). Red circles indicate seizure onset patterns in iEEG recording. Red vertical line in the top plot indicates seizure onset time. Red rectangle indicates the activities in the least involved channels, which are magnified in the bottom plot.

'loss of consciousness', which starts at score 3 (Arthuis et al., 2009). The higher the score is greater is the impairment or loss of consciousness (LOC).

Another important difference our work has with that of Arthuis and coworkers (Arthuis et al., 2009) is in bands of analysis. We did sub-band analysis contrary to Arthuis and coworkers. We undertook study of synchronization vis-à-vis loss of consciousness in delta, theta,

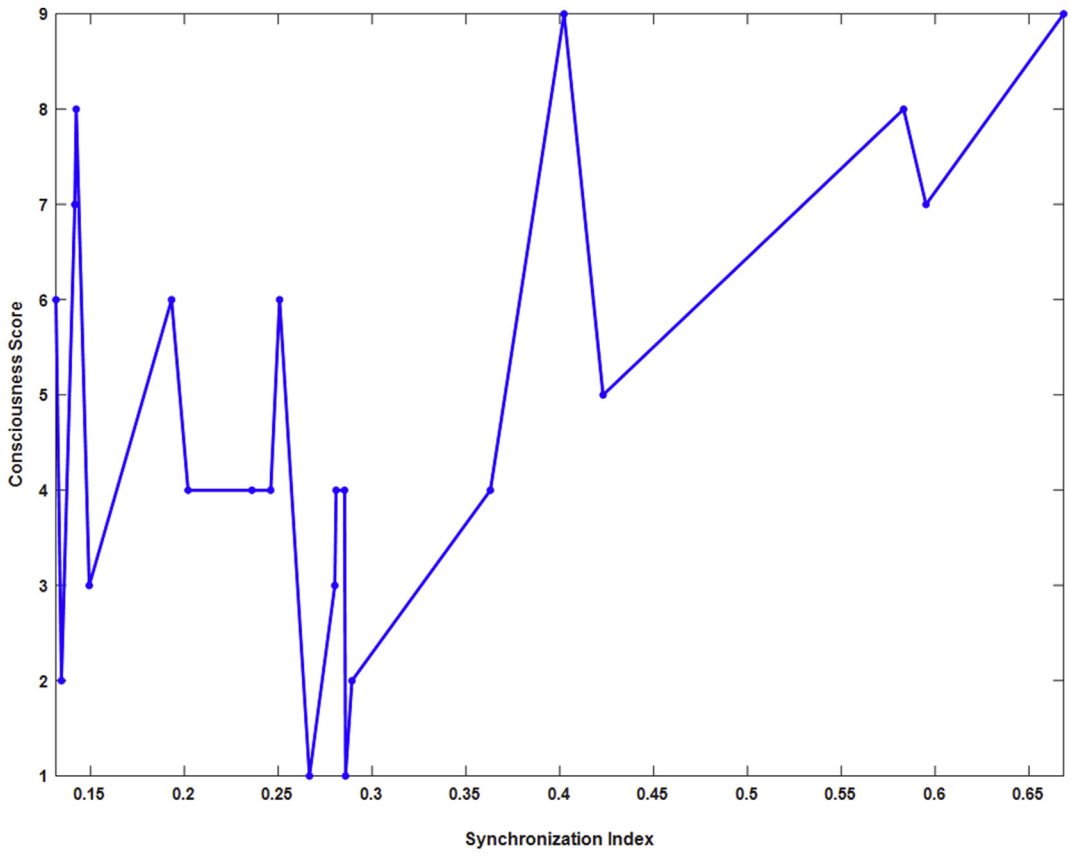

Figure 6. Synchronization index (mutual information across all the SOZ channels in 0–1 scale) arranged in increasing order versus consciousness score (in 1–9 scale) plot of 22 seizures with impaired consciousness recorded in 11 patients. Correlation between the two measures is 0.44 ($p < 0.05$), albeit the relationship between the two is not linear.

alpha, beta and gamma bands. The relationship is most prominent in gamma band, which is implicated in sensory awareness and consciousness in several studies (Engel et al. 1999, 2004; Doesburg et al., 2009).

The maximum score reached during seizures. In our study, we included only those seizures for which the bedside evaluation was initiated during the seizure. The examination protocol (see method section) was repeated by the bedside nurse during the seizure and the highest consciousness score was used in the study.

4.2. Extension

We extended the study of LOC associated with CPS undertaken by Arthuis and coworkers (Arthuis et al., 2009) in several ways. (1) Synchronization measure by h-square was repeated on our dataset along with 5 other synchronization measures. (2) All these measures are bivariate. We extended them to more than two variables. Since these multivariate measures are extremely RAM intensive, we had to restrict our analyses to SOZ channels and the least involved channels, where former are temporal and latter are extra-temporal. Total number of channels in our data from 11 patients was between 150 and 240 and therefore it was not possible to compute all the pairs. (3) We have tried to establish a causal relationship between enhanced synchronization in the latter half of seizure and the loss of consciousness in case of CPSs. Our results suggest that, only synchronization due to mutual information is associated with loss of consciousness in a statistically significant manner. (4) We have measured the synchronization in all the frequency bands namely, delta, theta, alpha, beta and gamma. Statistically significant synchronization was observed across the SOZ channels, by five out of the six synchronization measures that we have studied here, only in the gamma range (Table 2). Synchronization in gamma band has been widely implicated in cognition and consciousness (Engel et al. 1999, 2004; Doesburg et al., 2009).

Unlike Arthuis et al., 2009 we could not include thalamus and parietal cortex for clinical constraints. But since synchronization across the SOZ channels was quite significant in beta and gamma range, they likely have spread to wider brain areas (Kopell et al., 2000), supporting the study of Arthuis et al., (2009).

Table 4. Statistical significance values (p values) at beta, gamma range for consciousness impairment due to enhanced synchronization by 6 different measures.

	Amplitude correlation	Coherence	Mutual information	Phase locking value	Phase synchronization	Nonlinear correlation (h^2)
Beta	0.191	0.191	0.33	0.191	0.668	0.668
Gamma	0.5	0.5	*0.0946*	0.5	0.33	0.33

Statistically significant values (with $p < 0.1$) are marked with italic.

Table 5. Synchronization across SOZ channels is preceded by synchronization across LICs.

	Amplitude correlation	Coherence	Mutual information	Phase locking value	Phase synchronization	Nonlinear correlation (h^2)
Delta	0.9199	0.1723	**0.0459***	0.0948	0.4466	0.9329
Theta	0.1723	0.3770	**0.0006****	0.4348	0.2226	0.7590
Alpha	0.6783	0.9944	0.4703	0.0948	**0.0281***	0.7200
Beta	0.3884	0.5534	0.2410	0.8277	0.1802	0.3110
Gamma	0.4584	0.3325	**0.0107***	0.0897	**0.0374***	0.1297

p values by Wilcoxon signed rank test (right tailed) that are less than 0.05 have been marked with bold. $p < 0.01$ is marked by * and $p < 0.05$ by **. Also see analysis of Sz1 to Sz23 in the Supplementary material.

4.3. Synchronization in delta band

It has been reported that, slow delta wave activity (1–2 Hz) in the bilateral frontal and parietal cortices during complex-partial seizures coupled with unilateral mesial temporal fast seizure activity spreading to the bilateral temporal lobes, might be responsible for impaired consciousness (Englot et al., 2010). Higher synchronization across the channels in temporal lobe in beta and gamma range during the latter half of CPS is indicative of the propagation of the fast seizure activity in the temporal lobe. However, by all synchronization measures that we studied in this work the delta band synchronization within the temporal lobe remained insignificant (Table 2). This means there is no delta wave propagation from temporal lobe to frontal lobe and the emergence of delta wave in these extra temporal sites may reflect a result of network inhibition of brainstem and arousal network in accordance with network inhibition hypothesis (Englot et al., 2010). Human cortical slow wave studies are mostly associated with sleep and scalp EEG (Riedner et al., 2007). Large scale computer simulation of a thalamocortical system showed that decrease in synaptic strength lead to decrease in slow wave (0.5–4 Hz) activity. Decrease in synaptic strength may be a result of poorer neuronal synchronization (Riedner et al., 2007).

4.4. Synchronization in beta and gamma bands

One important finding is synchronization by most methods in beta and gamma range across the SOZ channels is more towards the seizure offset than at the beginning (Table 2 and Figure 4), whereas the highest synchronization is attained across the LICs ahead of the SOZ channels (Table 5). This trend has been observed in the gamma band, particularly by phase synchronization and mutual information. High synchronization leading to seizure termination has already been observed in multiple studies (Schindler et al., 2007; Jiruska et al., 2013; Prasad et al., 2013; Majumdar et al., 2014). During the course of this work, we have observed that high synchronization often persists beyond termination from least involved channels to SOZ in beta and gamma bands and impairs consciousness (results not presented).

Interestingly, gamma (Fries, 2009) and beta (Spitzer and Haegens, 2017) rhythms have been implicated mostly in conscious information processing by the brain. It has been shown that fast activity (at the beta range) across both hemispheres in the temporal lobe along with slow (1–2 Hz) activity in the fronto-parietal region leads to loss of consciousness during complex partial temporal lobe seizures (Englot et al., 2010). Clearly, beta-band synchronization across the temporal lobe is likely to be high during the seizure. In Table 2 we can see beta-band synchronization during the offset (second half of the seizure) is significantly high by 4 out of 6 synchronization measures. However, this could not be established as the possible cause of impaired consciousness in a statistically significant manner (Table 4) by any of the six synchronization measures we have studied here.

Statistically, in our study, the relationship between abnormally high synchronization and loss of consciousness has only been weakly established. Out of all six measures of synchronization, only enhanced value of mutual information in gamma band during the second half of seizure across the temporal lobe SOZ channels (preceded by enhanced synchronization across the frontal lobe LICs) had a statistically significant association with higher consciousness score ($p < 0.1$). In our opinion, this p-value indicates a weak statistical significance (although $p < 0.05$ is more common, $p < 0.1$ the significance level has also been used (Sterne et al., 2000)). Enhanced synchronization by any other measure out of the six we studied here, including the nonlinear correlation or h^2, which has been used in Arthuis et al., (2009), could not be associated with impaired consciousness in a statistically significant way. We have calculated the cross-correlation between consciousness score and synchronization (Figure 6), which was significant (0.4, $p < 0.05$). This means the two quantities are weakly correlated, and this conclusion is statistically significant. However, the underlying assumption is that the two quantities are linearly dependent, which is not true as evident from Figure 6. By formula (2) we also have been able to weakly associate the two quantities ($p < 0.1$). It is worth mentioning here that the relationship between the consciousness score and thalamo-cortical synchrony in Arthuis' paper (Arthuis et al., 2009) is also nonlinear.

4.5. Temporal lobe and consciousness

We have used here the consciousness scoring scheme introduced by (Arthuis et al., 2009) to assess the state of consciousness of the patients. However, there seems to be no straightforward (or linear, to be more precise) relationship between the level of synchronization and the level of consciousness (Figure 6). It was reported that excessive synchronization across wide brain regions during CPS is responsible for the loss of consciousness (Arthuis et al., 2009). But if synchronization is high, the loss of consciousness may not be as high and also the other way round. The relationship is dependent on many factors, like recording sites, exact onset zone and its propagation network for a particular seizure, etc.

4.6. Impaired consciousness in temporal lobe seizures

The temporal lobe is minimally implicated in consciousness. Here we have measured synchronization across the SOZ channels (which are in the temporal lobe).Our data have shown peak synchronization in the gamma band reaches in the extratemporal region (frontal lobe in our study) ahead of the temporal region, where synchronization has been measured by mutual information, which is a nonlinear measure. Empirically, this is observed in the majority of the cases by all measures of synchronization, but only statistically significant for mutual information and that too with a p-value 0.1, not 0.05 as widely practiced. Enhanced gamma band mutual information in the frontal lobe during the seizure may start interfering with consciousness and contribute to LOC. Our results are in agreement with prior studies that have hypothesized that frontal lobe dysfunction contributes to LOC in temporal lobe seizures.

5. Conclusion and future directions

Temporal lobe seizures can lead to loss of consciousness, but studies incorporating quantitative methods to elucidate the underlying mechanisms are rare, if at all. Here using six generalized (multivariate) synchronization measures, we demonstrate that changes in mutual information hold good promise to understand seizure-induced loss of consciousness. Abnormally high mutual information in the gamma band towards the end of temporal lobe seizures is associated with loss of consciousness in a weakly statistically significant way ($p < 0.1$). A novel association between consciousness score and synchronization measure has been worked out, which may be quite useful in other studies. We have followed a permutation motif based implementation of mutual information, where motifs are units of information encoding in the discrete signals. The study of loss of consciousness with seizure may be clinically important for developing a therapy to restore consciousness.

Future investigations should include EEG signals from the thalamus and parietal cortex, which are implicated in consciousness. Synchrony between these two regions has been investigated by Arthuis and coworkers (Arthuis et al., 2009), but we didn't sample those regions, which is a limitation of the current work. The methods developed in the current work will make the study much more precise. It may be worth investigating the relationship between delta band synchronization in frontal and parietal cortices and beta and gamma band synchronization in unilateral temporal lobe SOZ with respect to the loss of consciousness. This will be an extension of the work reported in Englot et al., (2010).

Declarations

Author contribution statement

Puneet Dheer: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Sandipan Pati, Kaushik Kumar Majumdar: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Kalyan Kumar Chowdhury: Contributed reagents, materials, analysis tools or data.

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Data availability statement

The authors do not have permission to share data.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

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