Sources and sinks nodes in absence seizures

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Abstract

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1 Introduction

Absence seizures are characterized by generalized 3Hz spikewaves whose emergence is believed due to a feedback loop interaction between thalamus and cortex [15]. More recent studies are putting this mechanism of generation of absence seizures into question [19, 18] by suggesting a more important role played by the cortex.

Since patients with absence seizures usually are not candidates for surgery, attention is devoted to seizure event detection via non-invasive techniques such as the EEG whose time series we analyze here for insights about patient condition as inferred by directed connectivity analysis and its meta-analysis with help networks summarized via graph theoretical measures [22].

Network inference defines the kind of graph measure that can be employed. Some such measures require estimating the directionality of connection information flow whereas other measures take into account link weights representing interaction strength. In this work we will employ a single measure that allows inferring networks that are at once directed and whose weights represent frequency domain coupling strengths for patients with episodic absence seizures. Networks inference is carried out at 3Hz, which is where EEG signal spectra peak for these patients. IThis also ensures spurious connection free graphs and prevents artifacts due other frequencies.

By analyzing these networks at 3Hz we show patterns of causal interactions between brain regions that suggest a more important role is played by some sites during the course of the seizure. Furthermore, since we have interaction directionality, we not only investigate the sources of causal interactions but also the regions that are targets of the driving nodes which together present a characteristic pattern during the ictal period.

2 Materials and methods

2.1 Data

The data analyzed were multivariate EEG signals, using 20 electrodes and following the International 10-20 System from 8 patients with absence seizures. The signal was acquired at a rate of 256 Hz and then partitioned into windows lasting 5 seconds each with an 80% time overlap between them. One seizure per patient was analyzed, with 5s long time windows before seizure start and another equal window after seizure end. Ictal period duration varied from 5 to 33 seconds.

For each time window, the connectivity matrix was inferred using both iPDC and GC from the Matlab package AsympPDC v3 [] considering $\alpha = 0.01$. In order to ensure data stationarity, possi-

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ble signal linear trends were removed by taking the first time difference. Autoregressive model was estimated through AIC and ranged from 4 to 9.

2.2 Causality Inference

An approach to estimate causal relationships from one neuronal population to another is through estimating the predictability of the activity of on one region onto the activity of another. The statistical framework that allow us to verify these relationships is called Granger causality testing (GC) which is beginning to be systematically applied in various studies in neuroscience [6]. Since causal influences between brain regions is often related to oscillatory behaviour, methods to infer causal relations in frequency domain have been proposed, among them, the Partial Directed Coherence (PDC) which is based on the fourier transformed coefficients from the multivariate auto-regressive model [3]. A comparison between different measures of causality in frequency domain can be found in [].

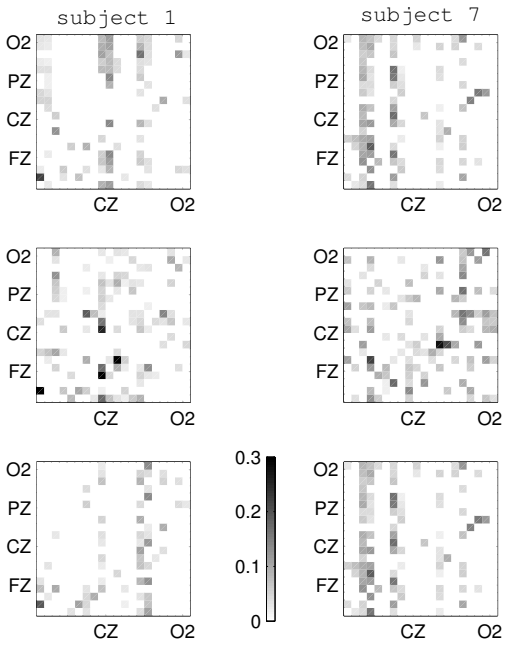

Figure 1: Adjacency matrices inferred using iPDC for frequency 3Hz. Upper frame left is for a time window before seizure for subject 1, upper right is before ictal for patient 7, mid left and mid right are matrices during inferred using the first 5 seconds of ictal, bottom left and bottom right are after the ictal end. The gray levels are the intensity of causal relationship.

3 Results

Figure 1 shows an example of the inferred connectivity matrices at 3 Hz for two patients. Note the high level of intra-personal difference between them, which, however changes into a fair degree of similarity after the seizure with respect to the similarity of the connectivity before seizure onset. Even with this level of variability some patterns can be found by investigating these matrices. A survey of the findings of epileptic networks can be seen in [15, **?**].

spectrum is concentrated at this band []. In this way, these matrices will be free from connections related with other brain activities or undesirable relations, for example, spurious connections from noise or movement artifacts.

iPDC shows an increase in the causal relationship between the signals during ictal period.

An advantage of iPDC over GC is its ability to measure the intensity of causal relation on a frequency region basis. Exploring this feature can help understand link network dynamics, an often neglected feature, since most current research work focus on evolving epileptic networks with their global topological patterns and characteristics as measured from considering the nodes (electrodes) the central elements of interest[15].

Figure 2 shows the mean of each iPDC connectivity matrix over time. Note the increase in mean intensity during the seizure and its return to preseizure levels after the seizure is over. This behavior is probably related with the hypersynchronization during the ictal period, where coupling between signals becomes most intense. Performing a left sided Wilcoxon signed rank test to check if the medians are equal against the alternative hypothesis that it is less than zero returned p-value 0.003 indicating there is enough evidence to conclude that the me-

dian before the ictal is less than the median after it.

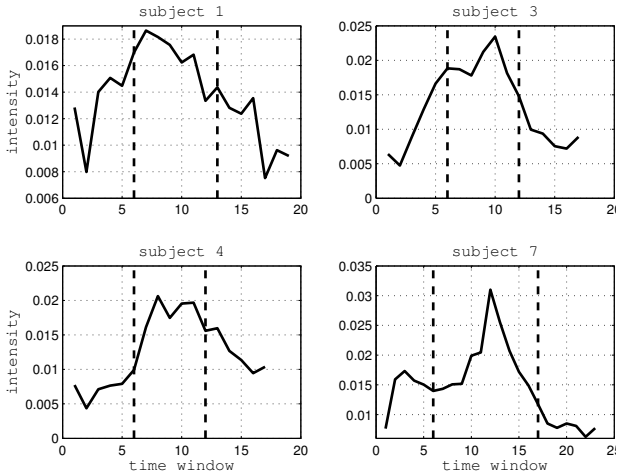

Figure 2: Mean of the iPDC intensity along time, the vertical lines points to the start and end of the ictal.

Some nodes present source behavior during seizure.

Since the previous feature of higher intensity during seizure was calculated by the mean of the matrix, it was a coarse approximation of the whole causal interactions. In order to see the evolution of the causal links, for each time window, the weighted avarage of the out-connections of each node were calculated as shown in Figure 3 which portrays the connection dynamics in terms of connection weights on a per-channel basis. This avarage considered only links which were significant, then, for each connectivity matrix M, from time window t, the avarage for each channel j is expressed by $w_{t,j} = \sum_i M_{i,j}/n_j$ where n_j was the number of significant out-degree connections for electrode j. Note that in all subjects, some regions have strong out-connection during the seizure, these nodes present a hub-like behavior, in other words, they are important nodes that are driving the others. The boxplots gives an idea about the of presence of outliers, nodes with higher out-degree than the mean.

The GC is closely associated with the concept of information flow [5, 8], in this way, these hubs

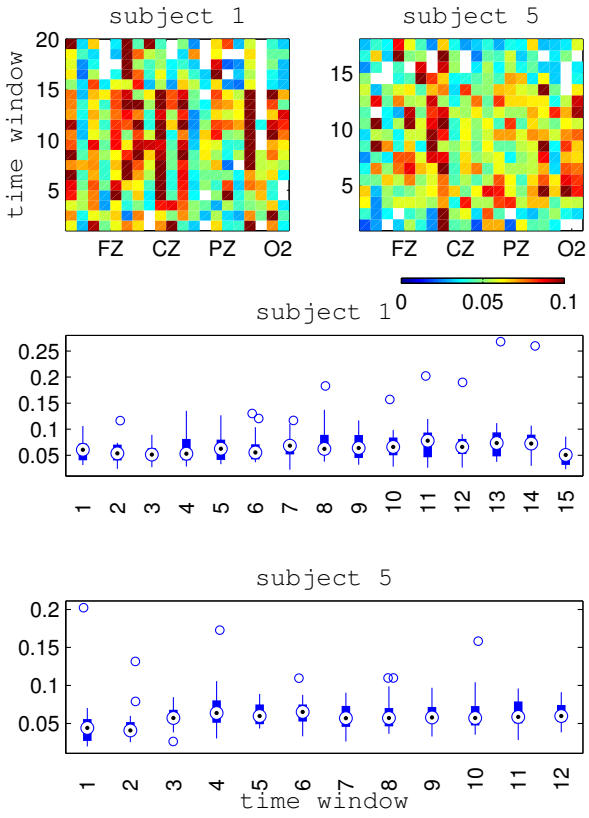

Figure 3: Avarage of causal interaction for each node along time. Some regions shows higher causal interactions than others (columns) which the duration of this behavior is limited to the duration of ictal. The seizure starts at time window 6.

can be interpreted as nodes with integrative informational role, connecting different regions and representing zones of convergence between specialized modules of neural processing [20]. This mechanism of integration are responsible for the emergence of synchronization and others dynamical patterns which are a common feature in a healthy brain [25, 10]. In fact, hubs were also found in pre-ictal period, fig. 3 channel T7 from subject 5 was a hub after and during seizure, but as the causal itensity increases during seizure (see fig. **??**), more causal relations arises in a non-uniform way, instead, few nodes concentrates the most part of causal interactions during the seizure. This pattern of some brain

regions increasing the coupling with multiple others regions and retaining this behaviour until the seizure end, may be a signature of the process of epilepsy spreading.

The list of these hubs can be seen in table 3, where the electrodes that were classified as hubs are listed with how many times they have been classified over the entire period shown in parenthesis. The criterion for this classification was based in the number of times that the nodes are placed in the top 10% of avarage weights. It is noteworthy that a regular pattern of hubs occur during ictal (figure 3). For example, in the figure subject 1 has a visible column in P8 , indicating this region have higher weight values compared to that of the connection matrix mean that remains fairly unchanged throughout seizure duration.

Patient	Pre-ictal	Ictal
1	C3 (3), FZ(2)	P8 (8) C3 (4)
2	C4 (2), C3 (2)	F4 (9) FZ (8)
3	T2 (2), P4 (2), O1 (2)	T8 (3), P4 (3), O2 (3)
4	FP1 (2), T7 (3)	T8 (5), T7 (4)
5	T7 (2), OZ (2)	F8 (4), T7 (4)
6	P7(4), P8 (2)	OZ (10), P7 (10)
7	C3 (3), T8 (2), O2 (2)	FP1 (9) P3 (5)
8	FP1 (3), F7 (2), C4 (2),	P7(10, FP2(9)

Table 1: List of nodes identified as hubs for each patient for both pre-ictal and ictal periods.

To better visualize the behavior of these source nodes, see figure 4 where the sum of weights of two source nodes were plotted together with a non-source node for subject 1. This figure is represent a close-up view of the column for electrodes P8 and C3 which are sources and T8 which is a non-source node.

Note that the three curves present different dynamics, T8 (red dashed-dotted) has a low value during the seizure episode and changes little from its baseline behaviour from its pre-ictal state. By contrast the electrode C3 (black dashed) increases a little before the seizure and remains during the seizure and descreases back to its value when the seizure is over. P8 (blue solid) has a slow and constant trend of increasing from seizure onset with a subtle decrease on seizure end where it reaches a basal value that is similar to that of other nodes.

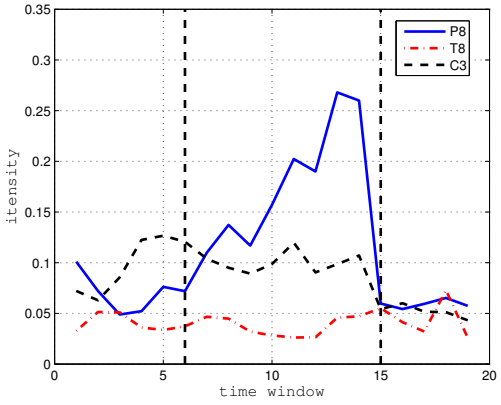

Figure 4: Evolution of sum of weights of two source and a non-source node along time. The sources nodes are the solid blue line P8 and the black dashed line C3. The non-source is the dashed-dotted red line corresponding to electrode T8. The vertical black dashed lines points to the start and ending of the seizure.

The distinct behaviour of these electrodes is likely to reflects an as yet unknown role for these brain regions and leads to some open questions: What's the role of regions that remain at the basal level? Are these regions necessary for synchronization phenomena? Are there different roles for source nodes? Can a node be more decisive during the seizure onset, making strong ties with the largest number of possible nodes, probably to start the phenomena while other nodes may have more steady coupling, related with maintenance of the hypersynchronization. This can bring a light to a novel way to classify the role of nodes as well a new way to characterize epilepsy from the viewpoint of network analysis.

A previous proposal to classify hubs considered the way which they are connected to other nodes, hubs with connections only to other nodes within the same community are called *provincial hubs* whereas hubs linking different modules are *connector hubs* [12]. This approach ignores the role of the node in the dynamics of the network and considers only the static topology of the graph, furthermore it's is valid only for networks which can be separated in communities. Another proposal classified hubs based in the way which they connects or modulates the activaction from others subnet-

works of the brain, revealing three types of nodes: default network-aligned, dorsal attention network-aligned and dual network-aligned nodes [26]. While this approach consider the dynamics between the networks, it's very specific in its domain and difficult to apply to other kinds of networks. A general method to rank the nodes according to theis dynamics still lacking and can improve to visualize and understand networks that evolve along time.

Until now, we discussed about the properties and occurrence of source nodes with high out-degree during absence seizures, but little is known about the way which these nodes are interacting with the seizure phenomena. Various theoretical results have demonstrated that networks with hub-like structure can lead to better synchronization in a complex network [13]. Simulation studies of rat models show that the inclusion of a high number of out-connection in certain nodes, transforms them into driver nodes that can lead to more enduring and intense seizures [21]. These studies suggests an active role in strenghthening or spreading the seizure by the hubs.

Other works evaluate the importance of high-degree nodes in brain communication and points to evidences that disruption of brain communication can be a determining factor in psychiatric disorders [28]. For example, studies in schizophrenia [16, 9, 2, 14, 1], autismo [24] and Alzheimer's disease [7, 27] points to an abnormal presence/ausence of hubs in patients with these disorders. As a consequence of being important to communication, there is a possibility of these nodes becoming a bottleneck of the information flow and thus, limiting the capacity of cognitive processing [23, 28, 17].

Moreover, the presence of clear local dynamics in certain brain sites, blends the definition of absence and focal epilepsy, as key characteristic of the former the lack of a clear seizure onset zone (SOZ). However, other studies in focal epilepsy show that only 35% of hubs found in network analysis of epilepsy signals are part of SOZ [11], pointing to a more important role of other brain regions at the start and later seizure spread. Maybe the source found in both focal and absence seizures are necessary to maintenance of the phenomena, and their presence is related with the synchronization dynamics.

Similarly, there are nodes that receive more causal influence.

A large number of works use complex networks measures to characterize the role of hubs in the networks and select these nodes as candidates to be analyzed and discussed, usually neglecting the targets of these nodes, or the sinks. A reason for this is the use of correlation and other symetrical methods to investigate connectivity [29], but leaving aside this properties can lead to an incomplete understanding of the phenomena in study.

In order to visualize the nodes that are targets of the causal relationships we did the same approach from previous results, but this time investigating the sum of the matrix lines. Figure 5 shows the evolution over time for the sum of PDC intensity for each electrode. Note that, again, there are nodes that receive more interaction than others, displaying an evident pattern. In subject 1, the regions from frontal cortex appears to have a stronger pattern along with electrode P7, while subject 7 has an interesting cluster on occipital lobe right at seizure onset that completely ceases at the end of seizure.

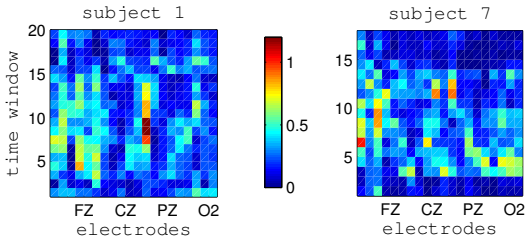

Figure 5: Evolution .

A edge centric approach

Instead of indentify and characterize only the source and sink nodes, a step further would be the analysis of the links on these important nodes. A edge centric approach may reveal more about the role of the nodes in a dynamical process, and, as the seizure has spatial properties, it can provide clues about the way that a node influences and reaches the other nodes from the network.

4 Conclusions

In this paper we performed a connectivity analysis of EEG signals from a patient with absence seizures. The analysis procedure inferred the adjacency matrices only for the main frequency that characterizes the phenomenon, limiting our scope to the band where the relations are more important and freeing the matrices from undesired connections from other neural activities, noise or artifacts. Moreover, the causality measure, being nonsymmetric, gives directionality information, which allowed exploring the source/sink feature of the nodes. These findings about important nodes in absence seizures suggests a more dynamic behaviour in this kind of epilepsy, with regions responsible for most of the causal relations while other regions are targets, being controlled by these driver nodes. These results are aligned with others studies on absence seizures showing that not only a subcortical structure is responsible by the seizure on-set, but that the cortex also plays an important role and is capable of showing behaviour similar to that of a focus [19, 18].

Furthermore, taking into account the sink nodes when analyzing networks dynamics can help understand the controlability features of these networks. Hubs are usually candidate brain sites in studies of stimulation [4], but what will be the effect if the sinks nodes were considered as candidates also? How should the dynamic be affected if the sinks were neutralized, will the sources still be operating? Answers to these questions can be useful for new types of treatment where hub like regions are sure to have important known roles.

As limitations of this study, we can point out exclusive use of scalp EEG, as something unavoidable since this medical protocol usually prohibits invasive investigative tecniques in absence seizure making this the best kind of data type avaliable. Another limitation was the low number of patients and short pre-ictal signal length, but we are still working to address these issues in future works. Possible next steps include comparing these source/sink nodes via other graph theoretical analysis measures, such as betweenness, and closeness and centrality and to extend the study to include focal epilepsy and verify if similar patterns are also present.

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References

[1] A. F. Alexander-Bloch, P. E. Vértes, R. Stidd, F. Lalonde, L. Clasen, J. Rapoport, J. Giedd, E. T. Bullmore, and N. Gogtay. The anatomical distance of functional connections predicts brain network topology in health and schizophrenia. *Cerebral cortex*, page bhr388, 2012.

[2] A. Alonso-Solís, I. Corripio, P. de Castro-Manglano, S. Duran-Sindreu, M. Garcia-Garcia, E. Proal, F. Nuñez-Marín, C. Soutullo, E. Alvarez, B. Gómez-Ansón, et al. Altered default network resting state functional connectivity in patients with a first episode of psychosis. *Schizophrenia research*, 139(1):13–18, 2012.

[3] L. A. Baccalá and K. Sameshima. Partial directed coherence: a new concept in neural structure determination. *Biological cybernetics*, 84(6):463–474, 2001.

[4] F. Bakouie, S. Gharibzadeh, and F. Towhidkhah. Managing epileptic seizures by controlling the brain driver nodes: a complex network view. *Frontiers in bioengineering and biotechnology*, 1, 2013.

[5] K. J. Blinowska, R. Kuś, and M. Kamiński. Granger causality and information flow in multivariate processes. *Physical Review E*, 70(5):050902, 2004.

[6] S. L. Bressler and A. K. Seth. Wiener–granger causality: a well established methodology. *Neuroimage*, 58(2):323–329, 2011.

[7] W. de Haan, K. Mott, E. C. van Straaten, P. Scheltens, and C. J. Stam. Activity dependent degeneration explains hub vulnerability in alzheimer's disease. *PLoS computational biology*, 8(8):e1002582, 2012.

[8] M. Dhamala, G. Rangarajan, and M. Ding. Analyzing information flow in brain networks

with nonparametric granger causality. *NeuroImage*, 41(2):354–362, 2008.

[9] A. Fornito, A. Zalesky, C. Pantelis, and E. T. Bullmore. Schizophrenia, neuroimaging and connectomics. *Neuroimage*, 62(4):2296–2314, 2012.

[10] P. Fries, D. Nikolić, and W. Singer. The gamma cycle. *Trends in neurosciences*, 30(7):309–316, 2007.

[11] C. Geier, S. Bialonski, C. E. Elger, and K. Lehnertz. How important is the seizure onset zone for seizure dynamics? *Seizure*, 2014.

[12] R. Guimera and L. A. N. Amaral. Functional cartography of complex metabolic networks. *Nature*, 433(7028):895–900, 2005.

[13] H. Hong, B. J. Kim, M. Choi, and H. Park. Factors that predict better synchronizability on complex networks. *Physical Review E*, 69(6):067105, 2004.

[14] H. Karbasforoushan and N. Woodward. Resting-state networks in schizophrenia. *Current topics in medicinal chemistry*, 12(21):2404–2414, 2012.

[15] K. Lehnertz, G. Ansmann, S. Bialonski, H. Dickten, C. Geier, and S. Porz. Evolving networks in the human epileptic brain. *Physica D: Nonlinear Phenomena*, 267:7–15, 2014.

[16] M.-E. Lynall, D. S. Bassett, R. Kerwin, P. J. McKenna, M. Kitzbichler, U. Muller, and E. Bullmore. Functional connectivity and brain networks in schizophrenia. *The Journal of Neuroscience*, 30(28):9477–9487, 2010.

[17] R. Marois and J. Ivanoff. Capacity limits of information processing in the brain. *Trends in cognitive sciences*, 9(6):296–305, 2005.

[18] H. Meeren, G. van Luijtelaar, F. L. da Silva, and A. Coenen. Evolving concepts on the pathophysiology of absence seizures: the cortical focus theory. *Archives of neurology*, 62(3):371–376, 2005.

[19] H. K. Meeren, J. P. M. Pijn, E. L. Van Luijtelaar, A. M. Coenen, and F. H. L. da Silva. Cortical focus drives widespread corticothalamic networks during spontaneous absence seizures in rats. *The Journal of neuroscience*, 22(4):1480–1495, 2002.

[20] K. Meyer and A. Damasio. Convergence and divergence in a neural architecture for recognition and memory. *Trends in neurosciences*, 32(7):376–382, 2009.

[21] R. J. Morgan and I. Soltesz. Nonrandom connectivity of the epileptic dentate gyrus predicts a major role for neuronal hubs in seizures. *Proceedings of the National Academy of Sciences*, 105(16):6179–6184, 2008.

[22] M. Rubinov and O. Sporns. Complex network measures of brain connectivity: uses and interpretations. *Neuroimage*, 52(3):1059–1069, 2010.

[23] M. Shanahan. The brain's connective core and its role in animal cognition. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 367(1603):2704–2714, 2012.

[24] F. Shi, L. Wang, Z. Peng, C.-Y. Wee, and D. Shen. Altered modular organization of structural cortical networks in children with autism. *PloS one*, 8(5):e63131, 2013.

[25] W. Singer. Synchronization of cortical activity and its putative role in information processing and learning. *Annual review of physiology*, 55(1):349–374, 1993.

[26] R. N. Spreng, J. Sepulcre, G. R. Turner, W. D. Stevens, and D. L. Schacter. Intrinsic architecture underlying the relations among the default, dorsal attention, and frontoparietal control networks of the human brain. *Journal of cognitive neuroscience*, 25(1):74–86, 2013.

[27] K. Supekar, V. Menon, D. Rubin, M. Musen, and M. D. Greicius. Network analysis of intrinsic functional brain connectivity in alzheimer's disease. *PLoS computational biology*, 4(6):e1000100, 2008.

[28] M. P. van den Heuvel and O. Sporns. Network hubs in the human brain. *Trends in cognitive sciences*, 17(12):683–696, 2013.

[29] A. Zalesky, A. Fornito, and E. Bullmore. On the use of correlation as a measure of network connectivity. *Neuroimage*, 60(4):2096–2106, 2012.