# Usage of network analysis to investigate Periodic Sharp Wave Complexes in EEGs of patients with sporadic CJD*

P. Lo Giudice[1], N. Mammone[2], F.C. Morabito[3], D. Ursino[3], U. Aguglia[4], V. Cianci[5], E. Ferlazzo[4], and S. Gasparini[4]

[1] DIIES, University "Mediterranea" of Reggio Calabria
[2] IRCCS Centro Neurolesi Bonino-Pulejo
[3] DICEAM, University "Mediterranea" of Reggio Calabria
[4] DSMC, University "Magna Graecia" of Catanzaro
[5] UOC Neurologia, Grande Ospedale Metropolitano di Reggio Calabria

**(DISCUSSION PAPER)**

**Abstract.** Creutzfeldt-Jacob Disease (CJD) is a rapidly progressive, uniformly fatal Transmissible Spongiform Encephalopathy. Sporadic CJD (sCJD) is the most common form of CJD. Electroencephalography (EEG) is one of the main methods to perform clinical diagnosis of CJD, mainly because of Periodic Sharp Wave Complexes (PSWCs). In this paper, we propose a new numerical coefficient and some network motifs, which characterize the presence of PSWCs in an EEG tracing. Furthermore, network motifs are able to detect what the most active and/or connected brain areas are in the tracing segments with PSWCs.

## 1 Introduction

Creutzfeldt-Jacob Disease (CJD) is a rapidly progressive, uniformly fatal Transmissible Spongiform Encephalopathy (TSE). It is characterized by the accumulation of a variant of the host encoded cellular prion protein in the brain [14]. CJD became well known to common people some years ago because one of its variants, known as vCJD, has been linked to the transmission of the causative agent of the bovine spongiform encephalopathy (BSE) to the human population, mainly in United Kingdom. Sporadic CJD (hereafter, sCJD) represents the most common form of CJD. An early and reliable diagnosis of CJD is extremely important to exclude other, potentially treatable, causes of rapidly progressive encephalopathies. However, the early diagnosis of this disease is complicated by the extreme heterogeneity of its clinical presentation. Electroencephalography (hereafter, EEG) has always been, and still is, one of the main methods to perform clinical diagnosis of neurological diseases in general [7], and of CJD in particular. In fact, in the EEG of patients with sCJD, it is often possible to observe three-phase periodic spikes with sharp waves known as "Periodic Sharp Wave Complexes" (hereafter, PSWCs). More specifically, PSWCs were reported

* Nadia Mammone's work was funded by the Italian Ministry of Health, Project Code GR-2011-02351397. This work was partially supported by Aubay Italia S.p.A.

to occur in the EEG tracings of about two-thirds of patients with sCJD. For this reason, they were included in the World Health Organization diagnostic classification criteria of sCJD [14, 13].

In the past, approaches to investigating PSWCs in the EEGs of patients with sCJD were mainly based on signal processing [14, 1, 12, 6]. By contrast, to the best of our knowledge, no network analysis based approach to investigating the CJD phenomenon has been previously proposed in the literature. Nevertheless, network analysis has been largely exploited in the investigation of brain, especially in those application scenarios where brain connectivity is extremely important [8]. For instance, in [9, 2], network analysis has been used to investigate Alzheimer's disease, whereas, in [10, 5], it has been employed to analyze Epilepsy. Since in sCJD (as well as in all the neurodegenerative diseases) the investigation of the connection level of the brain areas is extremely important, we argue that network analysis could play a key role in this research context. In this paper, we aim at providing a first contribution in this setting. Indeed, we propose a network analysis based approach to characterizing PSWCs in EEGs of patients with sCJD. Here, the term "characterizing" means two things, namely: *(i)* finding (if possible) a quantitative coefficient - that we call *connection coefficient* - capable of distinguishing the EEG tracing segments with PSWCs from the ones without PSWCs, and *(ii)* finding (possible) *network motifs* characterizing the presence (or, conversely, the absence) of PSWCs in an EEG tracing. In our opinion, these two contributions are worthwhile. Indeed: *(i)* A numeric coefficient can help to recognize PSWCs when they start to appear, thus allowing a much earlier diagnosis of sCJD. Furthermore, in the future, in presence of much more sophisticated electroencephalographs with 256 electrodes, the human eye could experiment much more difficulties in finding PSWCs. *(ii)* Motifs represent a further indicator of the presence of PSWCs. Furthermore, they could provide a characterization of the behavior of brain areas in presence of PSWCs. For instance, they could denote what the brain areas most connected and/or most active are in presence of PSWCs. This is, probably, the most important contribution of our approach because this information cannot be directly derived by a human expert.

This paper is organized as follows: in Section 2, we present some support data structures. In Section 3, first we illustrate our connection coefficient, then we introduce our concept of motif and, finally, we present our approach to motif extraction. Finally, in Section 4, we draw some conclusions.

## 2 Basic Support Data Structures

The EEGs to perform our investigation were provided by three different Italian centers (i.e., University "Magna Graecia" of Catanzaro, Neurologic Institute "Carlo Besta" of Milano, and Neurologic Institute of the University of Catania). They regard a group of ten patients with sCJD examined in the last 15 years

in these three centers[6]. We segmented each EEG at disposal in such a way as to separate the tracing segments with PSWCs from those without PSWCs. As a consequence, for each EEG, we had several tracing segments, which could be grouped in two distinct sets, namely, those containing PSWCs and those not containing PSWCs.

Formally speaking, let $EEGSet$ be the set of EEGs at our disposal, let $eeg$ be an EEG of $EEGSet$. Starting from $eeg$, it is possible to define a network $\mathcal{N}$ (resp., $\overline{\mathcal{N}}$) representing the set of segments of $eeg$ with PSWCs (resp., without PSWCs). Specifically: $\mathcal{N} = \langle V, E \rangle$ and $\overline{\mathcal{N}} = \langle V, \overline{E} \rangle$. Here, $V$ is the set of the nodes of $\mathcal{N}$ and $\overline{\mathcal{N}}$. Each node $v_i \in V$ corresponds to an electrode. In our EEGs, the electrodes were applied by following the 10-20 system. As a consequence, $|V| = 19$. $E$ (resp., $\overline{E}$) is the set of the edges of $\mathcal{N}$ (resp., $\overline{\mathcal{N}}$). Each edge $e_{ij} \in E$ connects the nodes $v_i$ and $v_j$. It can be represented as $e_{ij} = (v_i, v_j, w_{ij})$. Here, $w_{ij}$ is a measure of "distance" between $v_i$ and $v_j$, which is an indicator of their disconnection level. Actually, each measure representing this feature could be adopted in our model. In the experiments described in this paper, we adopted the *Permutation Disalignment Index* (PDI) between $v_i$ and $v_j$, which is a new metric of cross-randomness between channels in multivariate electrophysiological time-series [3].

In order to make our model more "user-friendly" and "expressive" and, at the same time, more capable of discriminating strong and weak connections between brain areas, we decided to construct two new networks, namely $\mathcal{N}_\pi$ and $\overline{\mathcal{N}_\pi}$, obtained from $\mathcal{N}$ and $\overline{\mathcal{N}}$ by removing the edges with an "excessive" weight and by coloring the other ones on the basis of their weight. More specifically, blue edges denote strong connections (i.e., small weights), red edges represent intermediate ones and, finally, green edges indicate weak connections. Due to space limitations, we cannot report the technical details concerning the construction of $\mathcal{N}_\pi$ and $\overline{\mathcal{N}_\pi}$.

In Figure 1, we report the colored networks $\mathcal{N}_\pi$ and $\overline{\mathcal{N}_\pi}$ for a patient with sCJD. The disposal of the nodes in the networks reflects the 10-20 system, even if they are rotated 90 degrees clockwise. Observe how the filtering of the edges with the highest distance, along with the coloration of the other ones on the basis of the closeness of the corresponding nodes, make this model very expressive. The trends emerging from these figures have been confirmed in all the other EEGs at our disposal. In particular, we observe that: *(i)* for a specific EEG, $\mathcal{N}_\pi$ has more edges than $\overline{\mathcal{N}_\pi}$; furthermore, the edges of $\mathcal{N}_\pi$ are generally stronger than the ones of $\overline{\mathcal{N}_\pi}$; *(ii)* in both networks, the strongest edges can be found in the occipital area of the skull.

[6] We are aware that the number of patients under examination is low. However, this is due to the fact that sCJD is a very rare disease and, consequently, it is very difficult to collect data about it.

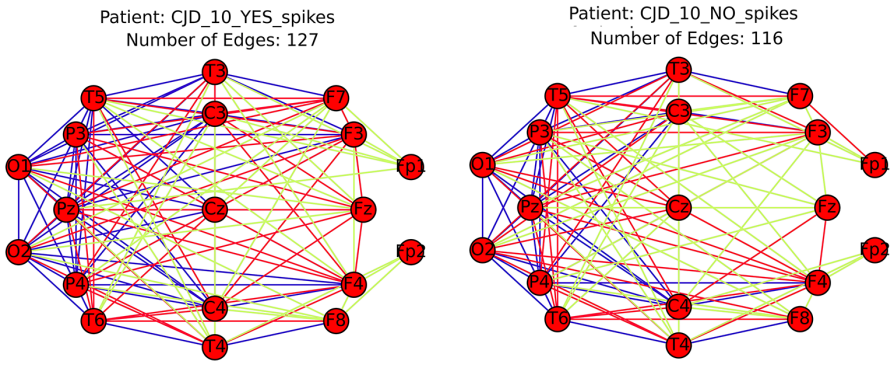


**Fig. 1.** Colored Networks $\mathcal{N}_\pi$ and $\overline{\mathcal{N}_\pi}$ for the patient CJD 10. Node labels reflect the electrode names in the 10/20 system

## 3 PSWC Characterization

### 3.1 Connection Coefficient

As pointed out in the Introduction, one of the main features to investigate in neurodegenerative patients is the connection level of brain areas. This feature is also relevant in the problem we are facing. In fact, in the literature, it was shown that, in presence of PSWCs, brain areas are more connected than in absence of them [11]. Furthermore, in Section 2, we have seen that the networks corresponding to the tracing segments with PSWCs are generally more and stronger connected than the networks corresponding to the tracing segments without PSWCs.

In network analysis, one of the most important (and, at the same time, simple and basic) tools for investigating network connection is the concept of *clique*. We recall that, given a network, a clique of dimension $k$ represents a totally connected subnetwork with $k$ nodes. On the basis of this reasoning, a quantitative coefficient for discriminating the networks corresponding to the tracing segments with PSWCs from the ones associated with the tracing segments without PSWCs could highly benefit from cliques.

In particular, this coefficient should take the following considerations into account: *(i)* Both the dimension and the number of cliques are important as connectivity indicators. *(ii)* The concept of clique is intrinsically exponential; in other words, a clique of dimension $n+1$ is exponentially more complex than a clique of dimension $n$.

Due to space limitations, we do not report here the technical description of connection coefficient. However, in Table 1, we report the values $cc_{\mathcal{N}_\pi}$ and $cc_{\overline{\mathcal{N}_\pi}}$ of this coefficient for $\mathcal{N}_\pi$ and $\overline{\mathcal{N}_\pi}$ , along with the percentage of decrease observed when passing from $cc_{\mathcal{N}_\pi}$ to $cc_{\overline{\mathcal{N}_\pi}}$, for all the patients at our disposal.

From the analysis of these tables we can draw two important results. In fact:

- $cc_{\mathcal{N}_\pi}$ is always higher than $cc_{\overline{\mathcal{N}_\pi}}$ except for the patient CJD 19 for whom the two coefficients have the same value. However, $\mathcal{N}_{\pi_{19}}$ and $\overline{\mathcal{N}_{\pi_{19}}}$ are associated

| Patient | $cc_{\mathcal{N}_\pi}$ | $cc_{\overline{\mathcal{N}_\pi}}$ | $\frac{cc_{\overline{\mathcal{N}_\pi}} - cc_{\mathcal{N}_\pi}}{cc_{\mathcal{N}_\pi}}$ |
|---|---|---|---|
| CJD 02 | 66064 | 24640 | -62.70% |
| CJD 04 | 20864 | 13312 | -36.20% |
| CJD 05 | 69632 | 43008 | -38.24% |
| CJD 08 | 196672 | 51712 | -73.71% |
| CJD 09 | 49664 | 25856 | -47.94% |
| CJD 10 | 20736 | 9728 | -53.09% |
| CJD 13 | 12288 | 5376 | -56.25% |
| CJD 16 | 9721 | 9216 | -5.19% |
| CJD 19 | 524288 | 524288 | 0% |
| CJD 22 | 164352 | 78080 | -52.49% |

**Table 1.** Values of $cc_{\mathcal{N}_\pi}$, $cc_{\overline{\mathcal{N}_\pi}}$ and $\frac{cc_{\overline{\mathcal{N}_\pi}} - cc_{\mathcal{N}_\pi}}{cc_{\mathcal{N}_\pi}}$ for all the patients at our disposal

with a very particular EEG. Indeed, $\mathcal{N}_{\pi_{19}}$ is totally connected and, therefore, has only a unique clique coinciding with it. $\overline{\mathcal{N}_{\pi_{19}}}$, instead, is totally connected except for only one edge; as a consequence, it has only two cliques, each consisting of 18 nodes.

As a consequence, we can say that connection coefficient is really a quantitative parameter capable of distinguishing the tracing segments with PSWCs from the ones without PSWCs.

– The values obtained for $cc_{\mathcal{N}_\pi}$ and $cc_{\overline{\mathcal{N}_\pi}}$ confirm the previous results presented in the literature about the fact that brain areas are more connected to each other in presence of PSWCs than in absence of them [11].

### 3.2 Motifs

Motifs were already investigated and exploited in past approaches adopting network analysis. In those scenarios, motifs are considered as "patterns of interconnections occurring in complex networks at numbers that are significantly higher than those in randomized networks" [4] . In our approach, we use motifs in a completely different fashion. Indeed, we do not examine a unique complex network to find patterns frequently repeated therein. By contrast, we search for patterns appearing frequently in the networks corresponding to the tracing segments with PSWCs and being absent in the networks corresponding to the tracing segments without PSWCs, thus characterizing the former segment typology against the latter, and vice versa.

As will be clear in the following, our approach to deriving motifs exploits the support data structures introduced in Section 2, along with a further support network, strongly based on the clique concept, which we call clique network. The clique network $\mathcal{CN}$ (resp., $\overline{\mathcal{CN}}$) corresponding to $\mathcal{N}_\pi$ (resp., $\overline{\mathcal{N}_\pi}$) and to the set $\mathcal{C}$ (resp., $\overline{\mathcal{C}}$) of the cliques of $\mathcal{CN}$ (resp., $\overline{\mathcal{CN}}$), is defined as $\mathcal{CN} = \langle CV, CE \rangle$ and $\overline{\mathcal{CN}} = \langle \overline{CV}, \overline{CE} \rangle$. Here: *(i)* $CV$ represents the set of the nodes of $\mathcal{CN}$; there is a node $v_i \in CV$ for each node $v_i \in V$. A weight $w_i$ is associated with $v_i$; it represents the number of cliques of $\mathcal{C}$ in which $v_i$ is involved; *(ii)* $CE$ represents the set of the edges of $\mathcal{CN}$. There is an edge $(v_i, v_j, w_{ij}) \in CE$ if the edge $(v_i, v_j)$ is present in at least one clique of $\mathcal{C}$. $w_{ij}$ denotes the number of cliques of $\mathcal{C}$ in which $(v_i, v_j)$ is present; *(iii)* $\overline{CV}$ and $\overline{CE}$ are analogous to $CV$ and $CE$, but

| *Motifs* | | | | | |
|---|---|---|---|---|---|
| Cz-Fz-P4 | Fz-P4-Pz | Fz-O2-P4 | F4-O2-T6 | C4-F4-T6 | F4-P4-T6 |
| Cz-Fz-Pz | F7-P3-Pz | Cz-Fz-O2 | F7-O2-P3 | Fz-O2-Pz | P4-T3-T4 |
| F7-Pz-T5 | F7-Pz-T3 | F7-O2-Pz | F7-O1-Pz | F7-O2-T5 | F7-O2-T3 |
| F7-O1-O2 | Pz-T3-T4 | T3-T4-T5 | T3-T4-T6 | O2-T3-T4 | O1-T3-T4 |

**Table 2.** The basic motifs extracted by our approach

for $\overline{\mathcal{C}}$, instead of for $\mathcal{C}$. The edges of $\mathcal{CN}$ and $\overline{\mathcal{CN}}$ can be "colored" in a way analogous to the edges of $\mathcal{N}_\pi$.

After having introduced clique networks, we define more restrictive colored networks and clique networks by removing green edges from the networks defined previously. Specifically, we define $\mathcal{N}_{\pi\pi}$, $\overline{\mathcal{N}_{\pi\pi}}$, $\mathcal{CN}_{\pi\pi}$ and $\overline{\mathcal{CN}_{\pi\pi}}$. We also define the sets $NSet_\pi$ (resp., $\overline{NSet_\pi}$, $NSet_{\pi\pi}$, $\overline{NSet_{\pi\pi}}$, $CNSet_{\pi\pi}$, $\overline{CNSet_{\pi\pi}}$) comprising all the networks $\mathcal{N}_\pi$ (resp., $\overline{\mathcal{N}_\pi}$, $\mathcal{N}_{\pi\pi}$, $\overline{\mathcal{N}_{\pi\pi}}$, $\mathcal{CN}_{\pi\pi}$, $\overline{\mathcal{CN}_{\pi\pi}}$) associated with the EEGs of $EEGSet$. Finally, let $t$ be a generic triad. We call $nocc_\pi$ (resp., $\overline{nocc_\pi}$, $nocc_{\pi\pi}$, $\overline{nocc_{\pi\pi}}$, $cnocc_{\pi\pi}$, $\overline{cnocc_{\pi\pi}}$) the number of occurrences of $t$ in $NSet_\pi$ (resp., $\overline{NSet_\pi}$, $NSet_{\pi\pi}$, $\overline{NSet_{\pi\pi}}$, $CNSet_{\pi\pi}$, $\overline{CNSet_{\pi\pi}}$).

After having defined all support data structures and parameters, we are able to describe our motif extraction approach. It consists of two main steps, the former devoted to the extraction of basic motifs and the latter conceived to the construction of derived ones. Preliminarily, it is necessary to specify what is a basic motif in our context. Specifically: let $t$ be a totally connected triad of $NSet_\pi$. If: (1) $t$ is present *frequently* in $NSet_\pi$ and is *absent* in $\overline{NSet_\pi}$, and (2) this trend is confirmed (also only to a lesser extent) for $NSet_{\pi\pi}$ and $\overline{NSet_{\pi\pi}}$ and also for $CNSet_{\pi\pi}$ and $\overline{CNSet_{\pi\pi}}$, then $t$ is a basic motif. In particular, $t$ is a motif characterizing the tracing segments with PSWCs against the ones without PSWCs.

In order to quantify the concept of "frequently", we define a threshold $th_f = \alpha_f \cdot |NSet_\pi|$[7]. In this case, Condition (1) becomes $(nocc_\pi \geq th_h) \wedge (\overline{nocc_\pi} = 0)$, whereas Condition (2) becomes $(nocc_{\pi\pi} > \overline{nocc_{\pi\pi}}) \wedge (cnocc_{\pi\pi} > \overline{cnocc_{\pi\pi}})$.

In a dual fashion, it is possible to define the basic motifs associated with $\overline{NSet_\pi}$ and characterizing the tracing segments without PSWCs against the ones with PSWCs. In the following, we indicate by $\mathcal{M}_\pi$ (resp., $\overline{\mathcal{M}_\pi}$) the set of motifs extracted starting from the triads of $NSet_\pi$ (resp., $\overline{NSet_\pi}$). In an analogous way, it is possible to derive the basic motifs of the sets $\mathcal{M}_{\pi\pi}$, $\overline{\mathcal{M}_{\pi\pi}}$, $\mathcal{CM}_{\pi\pi}$ and $\overline{\mathcal{CM}_{\pi\pi}}$, obtained starting from the triads of $NSet_{\pi\pi}$, $\overline{NSet_{\pi\pi}}$, $CNSet_{\pi\pi}$ and $\overline{CNSet_{\pi\pi}}$. The basic motifs derived by our approach are reported in Table 2.

Once basic motifs have been extracted and a first version of $\mathcal{M}_\pi$, $\overline{\mathcal{M}_\pi}$, $\mathcal{M}_{\pi\pi}$, $\overline{\mathcal{M}_{\pi\pi}}$, $\mathcal{CM}_{\pi\pi}$ and $\overline{\mathcal{CM}_{\pi\pi}}$ has been obtained, it is possible to construct derived (and, possibly, much more complex and significant) motifs starting from them.

Our approach to constructing new derived motifs starts from the already known ones. It uses nodes common to two or more known motifs as "junction points". Formally speaking, let $m_1 = \langle V_1, E_1 \rangle$ and $m_2 = \langle V_2, E_2 \rangle$ be two motifs of $\mathcal{M}_\pi$ such that $V_1 \cap V_2 \neq \emptyset$. Then, it is possible to construct a candidate

[7] We experimentally set the value of $\alpha_f$ to 0.30.

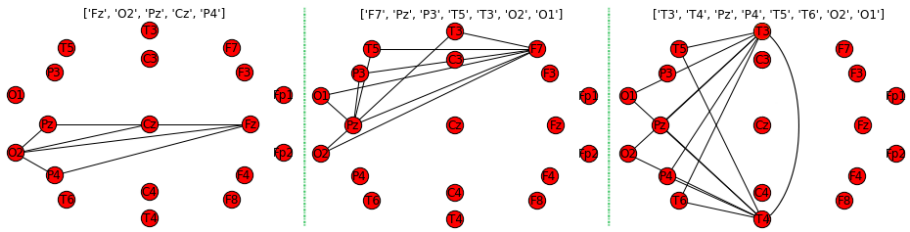


**Fig. 2.** The most significant motifs characterizing the tracing segments with PSWCs

motif as the union of $m_1$ and $m_2$: $m_{12} = \langle V_1 \cup V_2, E_1 \cup E_2 \rangle$. Once $m_{12}$ has been constructed, analogously to what we have seen for basic motifs, it is necessary to evaluate $nocc_\pi$, $\overline{nocc_\pi}$, $nocc_{\pi\pi}$, $\overline{nocc_{\pi\pi}}$, $cnocc_{\pi\pi}$ and $\overline{cnocc_{\pi\pi}}$[8]. If, for these parameters, conditions (1) and (2) presented above hold, then $m_{12}$ can be added to $\mathcal{M}_\pi$, i.e., $\mathcal{M}_\pi = \mathcal{M}_\pi \cup \{m_{12}\}$. Clearly, the addition of a new motif in $\mathcal{M}_\pi$ could lead to the possibility that new candidate motifs are constructed. As a consequence, the enrichment process of $\mathcal{M}_\pi$ is iterative and terminates when, during an iteration, no new motif is added to $\mathcal{M}_\pi$. In an analogous fashion, the derived motifs of $\overline{\mathcal{M}_\pi}$, $\mathcal{M}_{\pi\pi}$, $\overline{\mathcal{M}_{\pi\pi}}$, $\mathcal{CM}_{\pi\pi}$ and $\overline{\mathcal{CM}_{\pi\pi}}$ can be extracted.

In Figure 2, we report the most significant derived motifs extracted by our approach. The motif on the left derives from the tracing segments with PSWCs. It indicates that, in presence of PSWCs, the most active areas of the human brain reside in its right part. The other two motifs derive from the tracing segments without PSWCs. They indicate that, in absence of PSWCs, the most active areas of the human brain reside in its left part (motif on the center) and in its occipital part (motif on the right).

## 4 Conclusion

In this paper, we have proposed a network analysis based approach to characterizing PSWCs in EEGs of patients with sCJD. We have also introduced a new form of network motifs, well suited for this application context.

Clearly, this paper is only a first attempt of applying network analysis to characterize specific aspects of sCJD. In the future, we plan to investigate this possibility in more depth. As an example, the component of our approach performing motif extraction could be enriched in several directions. Furthermore, our approach does not currently perform analyses in the sub-bands $\alpha$, $\beta$, $\delta$ and $\theta$ of an EEG; adding this feature could be extremely useful, in particular for the sub-band $\delta$, which was proven to play a relevant role in the analysis of sCJD [14]. The ultimate goal of our research efforts could be a complete network analysis based decision support system, which can help a human expert in identifying patients with sCJD as early as possible starting from their EEGs.

[8] Clearly, for derived motifs, $nocc_\pi$, $\overline{nocc_\pi}$, $nocc_{\pi\pi}$, $\overline{nocc_{\pi\pi}}$, $cnocc_{\pi\pi}$ and $\overline{cnocc_{\pi\pi}}$ refer to the number of occurrences on motifs, instead of on triads.

## References


1. U. Aguglia, A. Gambardella, E. Le Piane, D. Messina, G. Farnarier, R.L. Oliveri, M. Zappia, and A. Quattrone. Disappearance of periodic sharp wave complexes in Creutzfeldt-Jakob disease. *Neurophysiologie Clinique/Clinical Neurophysiology*, 27(4):277–282, 1997. Elsevier.
2. W. de Haan, Y.A. Pijnenburg, R.L. Strijers, Y. van der Made, W. van der Flier, P. Scheltens, and C.J. Stam. Functional neural network analysis in frontotemporal dementia and Alzheimer's disease using EEG and graph theory. *BMC neuroscience*, 10(1):1, 2009. BioMed Central.
3. N. Mammone, L. Bonanno, S. De Salvo, S. Marino, P. Bramanti, A. Bramanti, and F.C. Morabito. Permutation Disalignment Index as an Indirect, EEG-Based, Measure of Brain Connectivity In MCI And AD Patients. *International Journal of Neural Systems*, http://dx.doi.org/10.1142/S0129065717500204, In press.
4. R. Milo, S. Shen-Orr, S. Itzkovitz, N. Kashtan, D. Chklovskii, and U. Alon. Network motifs: simple building blocks of complex networks. *Science*, 298(5594):824–827, 2002. American Association for the Advancement of Science.
5. F. Miraglia, F. Vecchio, G. Curcio, G. Della Marca, C. Vollono, E. Mazzucchi, and P. Rossini. Cortical connectivity in fronto-temporal focal epilepsy from EEG analysis: A study via graph theory. *Clinical Neurophysiology*, 127(3):e47, 2016. Elsevier.
6. F.C. Morabito, M. Campolo, N. Mammone, M. Versaci, S. Franceschetti, F. Tagliavini, V. Sofia, D. Fatuzzo, A. Gambardella, A. Labate, L. Mumoli, G.G. Tripodi, S. Gasparini, V. Cianci, C. Sueri, E. Ferlazzo, and U. Aguglia. Deep Learning representation from electroencephalography of early-stage Creutzfeldt-Jakob Disease and Features for Differentiation from Rapidly Progressive Dementia. *International Journal of Neural Systems*, 3:1650039, 2016. World Scientific.
7. V.P. Oikonomou, A.T. Tzallas, and D.I. Fotiadis. A Kalman filter based methodology for EEG spike enhancement. *Computer Methods and Programs in Biomedicine*, 85(2):101–108, 2007. Elsevier.
8. M. Rubinov and O. Sporns. Complex network measures of brain connectivity: uses and interpretations. *Neuroimage*, 52(3):1059–1069, 2010. Elsevier.
9. 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. Public Library of Science.
10. S. Supriya, S. Siuly, and Y. Zhang. Automatic epilepsy detection from EEG introducing a new edge weight method in the complex network. *Electronics Letters*, 52(17):1430–1432, 2016. IET.
11. R.D. Traub and T.A. Pedley. Virus-induced electrotonic coupling: Hypothesis on the mechanism of periodic EEG discharges in Creutzfeldt-Jakob disease. *Annals of Neurology*, 10(5):405–410, 1981. Wiley Online Library.
12. P.S. Wang, Y.T. Wu, C.I. Hung, S.Y. Kwan, S. Teng, and B.W. Soong. Early detection of periodic sharp wave complexes on EEG by independent component analysis in patients with Creutzfeldt-Jakob disease. *Journal of Clinical Neurophysiology*, 25(1):25–31, 2008. LWW.
13. World Health Organization (WHO). Consensus on criteria for diagnosis of sporadic CJD. *Weekly Epidemiological Record*, 73:361–365, 1998.
14. H.G. Wieser, K. Schindler, and D. Zumsteg. EEG in Creutzfeldt–Jakob disease. *Clinical Neurophysiology*, 117(5):935–951, 2006. Elsevier.