A game-theoretic analysis of network connectivity reveals that state transition is crucial for epilepsy surgery outcome prediction

Karla Ivankovic[1,2], Alessandro Principe[1,2,3], Justo Montoya[2], Linus Manubens-Gil[5], Mara Dierssen[1,2,6,7,†], Rodrigo Rocamora[1,2,3,†]

[†]These authors contributed equally to this work.

1 IMIM - Hospital del Mar Medical Research Institute, 08003 Barcelona, Spain

2 Universitat Pompeu Fabra (UPF), 08003 Barcelona, Spain

3 Epilepsy Unit - Neurology dept. Hospital del Mar - Parc de Salut Mar, 08003 Barcelona, Spain. Member of the European Reference Network EpiCARE.

4 University Pompeu Fabra, 08003 Barcelona, Spain

5 SEU-Allen Joint Center for Neuron Morphology, Southeast University (SEU), 210096 Nanjing, China

6 Centre for Genomic Regulation (CRG), 08003 Barcelona, Spain

7 Biomedical Research Networking Center on Rare Diseases (CIBERER), Institute of Health Carlos III, 28029 Madrid, Spain

Drug-resistant epilepsy patients are candidates for surgical intervention to remove the epileptogenic brain tissue. Despite the extensive presurgical workups, including invasive EEG, seizures recur in more than half of the operated patients. Improving the topological definition of epileptogenic networks is crucial, however, it remains a challenge due to the lack of a standard theoretical model of functional network dynamics. Here, we present a model illustrating the evolution of network connectivity leading to a seizure. Connectivity dynamics is modeled as a competition between two agents, which is assessed trough a game theoretic framework. When a seizure occurs, the epileptogenic network prevails, exhibiting greater connectivity change.

We designed a computational framework for identifying epileptogenic networks from invasive EEG data. Functional connectivity was quantified in the epochs of non-seizure, pre-seizure, transition to seizure, and seizure events. Epochs were compared between states (e.g., pre-seizure versus seizure) using a machine learning algorithm and the classification performance determined the connectivity change. A game theoretic decision rule was used to calculate the state of competition and identify the network with the greatest connectivity change. The overlap of the identified epileptogenic network and the actual surgical resection was used to predict surgery outcomes. We evaluated the framework in a consecutive cohort of 21 patients with a postsurgical follow-up of minimum 3 years.

The transition from pre-seizure to seizure was the optimal time frame for identifying the epileptogenic network. The identified networks overlapped with the actual resections significantly better in good outcome patients, in comparison to patients with poor outcomes. Surgery outcome prediction achieved 93% area under the receiver operating characteristic curve. The analysis of baseline connectivity changes also provided accurate surgery outcome prediction. Lastly, the ictal activity was the least informative as both epileptogenic and non-epileptogenic nodes exhibited great connectivity changes.

We present an analytical approach to electrophysiological data that allows topological definition of epileptogenic networks. Our results demonstrate that epileptogenic networks exhibit higher connectivity changes at state transition to seizure, as compared to non-epileptogenic nodes. The tools provided by this study may aid in surgical decision-making and potentially improve epilepsy surgery outcomes. In a broader perspective, our work demonstrated that connectivity can be usefully classified with a machine learning analysis and provide information for distinguishing a separate functional network. The findings from this study may serve as a reference for brain network connectivity models which are difficult to validate, such as those of cognitive processes.