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Original Research Article

Developing Biomarker for Neuronal-Instability in Epileptic Patients

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Conflict of interest: Nil

Abstract

Aim: The aim of present study was to design, develop and substantiate a modern contemporary biomarker for neuronal instability in epileptic (epilepsy) subjects (patients).

Methods: The present study was conducted in the Department of Neurology. The initial study was done on 100 subjects through the application of neuronal-unpredictability and/or variability of the marked epileptic seizure onset zone (e-So Z) as a metric to envisage and foresee the epileptic operational (surgical) outcome.

Results: We sought to test these theories by comparing high-frequency oscillation rates and networks in surgical responders and non-responders, with no appreciable change in seizure frequency or severity, within a retrospective cohort of the patients implanted with stereo-EEG electrodes. We recorded inter-ictal activity during non-rapid eye movement sleep and semi-automatically detected and quantified high-frequency oscillations. Each electrode contact was localized in normalized coordinates. We found that the accuracy of seizure onset zone electrode contact classification using high-frequency oscillation rates was not significantly different in surgical responders and non-responders, suggesting that in non-responders the epileptogenic zone partially encompassed the seizure onset zone(s).

Conclusion: In this study we attempted to develop a biomarker for the epileptic seizure onset zones. Within the eSoZ, the seizure is captured and then resection can be done accordingly. The source is highly influential on others yet extremely not affected by others. Therefore, the source and sinks within the epileptic seizure patients are the e-patients brains networks. So, think that brain is a complex yet nebulous neural-net-work, in which the nodes are connections, and the weights are the network branch edges (between node to node connection) that are dynamic. Thus, the source in the e-brain‘s neural-nets are within the sink only.

Keywords: Epilepsy, Seizure, Retrospective, Epileptic seizure, Biomarker.

Introduction

The brain is a complex network, evidenced by a plethora of neuroanatomic and neurophysiologic data ranging from microscale (at the neuron level) to macroscale (at the level of brain areas) studies. [1] One of the central nervous systems (neurological) disease and/or disorder is the epileptic seizures, or it usually is referred to as epilepsy (which can be referred to as seizure epilepsy) in which the subjects brain activities become abnormal and anomalous, thereby triggering, and set off seizures (convulsions also called as fibrillation potentials) or periods of unusual behavior, sensations and sometimes loss of awareness. [2] The drug resistant epileptic seizures (DRE) is characterized and well-defined as continued and thus repeated epileptic-seizures in even though spite of two tests of properly taken anti-epileptic drugs. [3]

Approximately 50% (of DRE-subjects) have focal (pointing) D R E, somewhere and at someplace of particular yet specific brain-region(s), referred to as the epileptogenic-zone (EZ), which is essential plus adequate for starting e-seizures and whose elimination (or disconnection and discontinuation) results in wide-ranging elimination of seizure-epilepsies [4,5] The network concept has been proposed as a key factor in identifying the anatomic distribution of the epileptogenic process, which is particularly important in the context of epilepsy surgery. [6] It also offers a framework to describe the dynamic course of seizures and their clinical expression. In contrast with other brain diseases, epilepsies are heterogeneous and involve unstable brain states (interictal vs. ictal). The definition of epileptic networks is also largely dependent on methodologic approaches. Epilepsies are characterized by altered brain rhythms; consequently, the study of electrophysiologic changes is crucial. [7] Focal epilepsy is the most common type of epilepsy. [8] Although seizure onset is confined to a focus comprising one or a few areas, several lines of evidence now

demonstrate that focal epilepsy is a network disorder with widespread influence rather than a disorder of an isolated area. [1,9]

Epilepsy affects both males and females of all races, ethnic backgrounds, and age. The past decade has seen an increasing consensus over the idea that epilepsy should be considered a network disease caused by coordinated activity across large-scale anatomical structures or functional connections of different brain regions. [10] The concept of an epileptogenic network has been proven by many methods, such as functional magnetic resonance imaging (fMRI), [11,12,13] diffusion tensor imaging (DTI), and computational models.[10] Through high-resolution mapping of biomarkers of epileptogenicity, electroencephalography (EEG), in particular intracranial electroencephalography (iEEG), allows for direct visualization of the epileptogenic network and its dynamic evolution in time. [14-16]

Resting-state EEG connectivity studies have also generated new knowledge about the outward connectivity of the EZ. Whereas, the bilateral posterior cingulate cortex (PCC) has been shown to have the highest outward connectivity in controls during resting state, the ipsilateral hippocampus had the highest outward connectivity in patients with temporal lobe epilepsy (TLE) using electrical source imaging from high-density EEG.[17] Hence, the main objectives of this study is to develop a seizure marker which is called a biomarker for tracing the epileptic seizure onset zone (eSoZ) in a region of the epileptic patient's brain.

Materials & Methods

The present study was conducted in the Department of Neurology, AIIMS Patna, Bihar, India for nine months. Initial study was done on 100 subjects through the application of neuronal-unpredictability and/or variability of the marked e-SoZ as a metric to envisage and foresee the epileptic operational (surgical) outcome.

A new biomarker for the identification of the epileptic seizure onset zone is developed and is followed very thoroughly underneath. Initially a simulation programme is built by using the mathematical frameworks. In analog EEG, the data is generated spontaneously ,dynamically and continuously (nonstop),therefore if there is any subtle change in those analog waveforms/signals, it is difficult for the clinician to pinpoint the error.

The EEG marker of SoZ,is referred to as neural-delicacy or fragility.

Top: i-EEG traces in the middle in between of seizures (Left) and in the course of seizure (during Right)

Bottom: NW schematic showing change in connectivity (Right) in delicacy (fragile) node which cause epileptic- seizure.

Insight of neural instability or delicacy – the upper left showing the intracranial EEG tracings amid the seizures, upper right showing during the seizures, bottom left showing the network schematic diagram with no change in the connectivity (balanced EEG network) followed by the unbalanced networks (right) showing the change in the connectivity (right) in delicate node which is causing the seizures. The concept of neural delicacy (fragility) in the framework of a dynamical intra cranial EEGs net-work, by the nodes- concept demonstrating the excitation (E, or excitatory) followed by the inhibition (I, or inhibitory concept) neurons populations. Now by applying through the high-end brain signal processing mathematics (i.e., dynamical-systems) point of view, such imbalance arises from a few delicate nodes and triggering uncertainty of the net-work like over-inflammation (or "excitation"), which can be called as "in low-inhibition". We derive the delicacy of a net- work node concept to be the "smallest-strength trepidation or distress utilized to the weight of the nodes upon its neighborhoods' prior to providing the executing the net- work unbalanced and unpredictable. [18,20] In systems theory, stable systems return to a baseline condition when a node is perturbed. Contrarily, unpredictable/unstable systems be able to fluctuate/oscillate plus increase and then produce as soon as a node is disturbed or disconcerted/(perturbed). In epileptic-seizures situations, a delicate-node is a node which needs a lesser alarm to cause e-seizure action and movement and a complete activities. The theory of delicacy or delicate nodes (fragility) be able to and capable to be developed in the framework of lineal/ (or linear) ordered sets like radial curves dynamical systems $x(t + 1) = Ax(t)$. Disquieting the column's of a matrix "A" can modify dynamically connected-networks of a certain and specific-node (i.e., of its column's) upon its neighborhoods, causing in an unjust ice net-work (un balanced). [18,19]

Results

Table 1: Results of generalized linear mixed-effects models fitting fR on O frequency in the different patient cohorts

Response variable	Intercept estimate	Intercept P-value	SOZ estimate	SOZ P-value	Location estimate	Location P-value
All patients from freq.	5.556 (5.51 5.60)	0	−0.081 (−0.086 −0.076)	0	0.016 (0.014 0.017)	0
Responders from freq.	5.470 (5.41 5.52)	0	0.178 (0.170 0.187)	0	0.012 (0.010 0.013)	0
Non-responders from freq.	5.646 (5.53 5.76)	0	−0.352 (−0.362 −0.343)	0	0.010 (0.008 0.011)	0
No resection or RNS from freq.	5.523 (5.47 5.58)	0	−0.004 (−0.015 0.008)	n.s.	0.014 (0.012 0.017)	0
All patients from freq.	5.591 (5.54 5.64)	0	−0.021 (−0.039 −0.003)	0.02	0.009 (0.005 0.012)	1 × 10−5
Responders from freq.	5.522 (5.45 5.60)	0	0.005 (−0.024 0.030)	n.s.	0.0175 (0.013 0.023)	0
Non-responders from freq.	5.613 (5.56 5.67)	0	−0.008 (−0.036 0.020)	n.s.	0.005 (−0.0005 0.01)	n.s.
No resection or RNS from freq.	5.768 (5.69 5.85)	0	−0.097 (−0.14 −0.05)	1× 10−5	−0.018 (−0.031 −0.005)	1 × 10−3

We sought to test these theories by comparing high-frequency oscillation rates and networks in surgical responders and non-responders, with no appreciable change in seizure frequency or severity, within a retrospective cohort of the patients implanted with stereo-EEG electrodes. We recorded inter-ictal activity during non-rapid eye movement sleep and semi- automatically detected and quantified high-frequency oscillations. Each electrode contact was localized in normalized coordinates. We found that the accuracy of seizure onset zone electrode contact classification using high-frequency oscillation rates was not significantly different in surgical responders and non-responders, suggesting that in non-responders the epileptogenic zone partially encompassed the seizure onset zone(s).

Discussion

One of the central nervous systems (neurological) disease and/or disorder is the epileptic seizures, or it usually is referred to as epilepsy (which can be referred to as seizure- epilepsy) in which the subjects brain activities become abnormal and anomalous, thereby triggering, and set off seizures (convulsions also called as fibrillation potentials) or periods of unusual behavior, sensations and sometimes loss of awareness. Anyone can develop epilepsy. Epilepsy affects both males and females of all races, ethnic backgrounds, and ages. In the beginning some authors they referred the seizures as positive sharp waves (sawtooth waveforms) have the same origin as convulsions of fibrillation potentials and have the same significance. [20-24]

We sought to test these theories by comparing high-frequency oscillation rates and networks in surgical responders and non-responders, with no appreciable change in seizure frequency or severity, within a retrospective cohort of the patients implanted with stereo-EEG electrodes. We recorded inter-ictal activity during non-rapid eye movement sleep and semi- automatically detected and quantified high-frequency oscillations. Each electrode contact was localized in normalized coordinates. We found that the accuracy of seizure onset zone electrode contact classification using high-frequency oscillation rates was not significantly different in surgical responders and non-responders, suggesting that in non-responders the epileptogenic zone partially encompassed the seizure onset zone(s). The prognosis after respective surgery in drug-resistant focal epilepsy is intricately dependent of the precise identification of an EZ subnetwork. By definition, the EZ is the ensemble of cortical regions that underlie the emergence of focal ictal activity and of which the removal, by surgical intervention, leads to the cessation of ictal activities, that is, to a patient's freedom from seizures. [25] In 30%–40% of all cases, seizures persist after surgery, and a major reason could be related to the fact that the EZ has not been correctly identified. [26] This difficulty is partly caused by the distributed network nature of the EZ. In the original work where the EI index was presented, when averaged over patients, the computed EI offered a clear distinction between the group of mesial structures (known to be involved in the EZ) and a second group of less epileptogenic lateral cortical structures, as values of EI obtained for the latter group were found to be significantly lower than those for the former group. However, within the mesial structures themselves, a gradient of EI values was observed, supporting the fact that the EZ cannot be easily delineated to few unique structures but rather manifests as a complex

network of distributed areas with variable epileptogenicity. [27] This further justifies the use of dynamical systems-based network analysis techniques in the analysis of seizure electrophysiological signals. The theoretical dynamical systems framework of seizure dynamics builds on a solid mathematical basis in bifurcation theory and has proven its power for the construction of personalized brain network models that are already potential tools for the guidance of epilepsy surgical interventions. [28] Clinical approaches across many laboratories have validated the framework for seizure dynamics empirically and laid out a taxonomy of dynamotypes for a classification of seizures based on dynamics. [29] It was shown that the stereotypy of the main elements of seizure onset signals (fast oscillations and spikes) can be interpreted as an indicator of the existence of invariant dynamical properties shared by different seizures. Moreover, by characterizing the scaling behavior of frequency and amplitude during seizure onset and offset, specific bifurcation types can be identified as the underlying dynamical mechanisms through which these transitions into and out of seizure states occur.

Conclusion

In this study we attempted to develop a biomarker for the epileptic seizure onset zones. Within the eSoZ, the seizure is captured and then resection can be done accordingly. The source is highly influential on others yet extremely not affected by the others. Therefore, the source and sinks within the epileptic seizure onset patients are the e-patients brains networks. So, think that brain is a complex yet nebulous neural-net-work, in which the nodes are connections, and the weights are the network branch edges (between node to node connection) that are dynamic. Thus, the source in the e-brain‘s neural-nets are within the sink only.

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