IP Indian Journal of Neurosciences 2022;8(4):248–253

Content available at: https://www.ipinnovative.com/open-access-journals

IP Indian Journal of Neurosciences

Journal homepage: https://www.ijnonline.org/

Original Research Article

Seizure epilepsy genesis and epileptogenic nodes in epileptic patients: A procedure

V Rama Raju[1,*], V Malsoru[2], K Srinivas[3], B. Kavitha Rani[3], G Madhukar[3]

[1]*CMR College of Engineering & Technology, Affili.: Jawaharlal Nehru Technological University JNTU, Hyderabad, Telangana, India*
[2]*Dept. of IT, CMR Technical Campus Kandlakoya, Hyderabad, Telangana, India*
[3]*Dept. of CSE, CMR Technical Campus, Kandlakoya, Hyderabad, Telangana, India*

ARTICLE INFO

Article history:
Received 28-11-2022
Accepted 17-12-2022
Available online 19-01-2023

Keywords:
Epilepsy
Seizure
Epilepticseizures
Eseizures
Dynamical systems
Delicate nodes
Fragile nodes
Epileptic seizure onset zone
eSoZ

ABSTRACT

In this study we attempted to design, develop and substantiate a modern contemporary biomarker for epileptic (epilepsy) subjects (patients) neuronal-instability. Initial study is done on 91 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. the neural-instability predict (42/45) subjects unsuccess with surgery, by a total accuracy of 75% (predictive) when matched with subjective-clinicians accuracy at 49%(results-effective). We differentiate instable zonal areas (zones) which were not diagnosed in unsuccessful cases (i.e., unsuccessful outcomes). While compared with EEG features, the neural-variability outpaced in prognosis strength and, also construal, which support that neuronal delicacy as a bio-marker for the electro encephalography e-SoZ.

1. Introduction

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.[1–8]

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] The epileptic subjects (patients) have an enhanced risk-of sudden and unexpectedly demise plus repeatedly hospitalized, hampered with epileptic-seizures connected incapacities and debilities, also their cost of care is a important donor to the $16 billion American dollars consumed per annum in the United States of America (USA) doctoring epileptic-patients.[4] 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.[5,6] The e-zone involves the medically (clinically) associated e-seizure

* *Corresponding author*.
E-mail address: drvenkateshwararrr@gmail.com (V. R. Raju).

https://doi.org/10.18231/j.ijn.2022.049

onset zone (e-SoZ) also early on proliferation zone(EPZ). Some areas and/or regions of human-brain cortical and sub cortical structures are associated through the eSoZ establish the initial and timeliest electro physiological changes throughout an e-seizure occurrence (event), plus in over-all herald the quantifiable clinical-experimental on set of e-seizures; and an early on proliferation/popagation zone(EPZ) areas are tangled during the time of the initial untimeliest clinical (semio-logical) features and signs and symptoms manifestation's throughout the event of the e-seizure. Successful surgical The neuro-(electro)-modulatory therapeutic-treatments might prevent the e-seizures largely or else let them yet to be prevent through the prescriptional-medicines/medications,[7] however the results for mutually therapeutic-treatments disparagingly be contingent on precise point of the e-S.o.Z.

Pinpointing the eSoZ also depend on the precise positioning of innocuous-electrodes such that they pass through the epileptic-seizure zone, plus the capability to determine the anomalies/ or deformities within the intra cranial EEG (i-EEG) electrode-channels that may correlated/ relate to the e-SoZ through the naked-eyes (focal). Regrettably, the much more qualified neurologists(clinicians) are confronted it is due to the epileptic-seizures are essentially and profoundly the net-work disease, that can't be solely characterized through presently existing procedures/methods and techniques of focusing or pinpointing. Anomalous links through a number of innocuous electrode-channels might represent a further successful biomarker of the e-S.o.Z.[8] Therefore, pinpointing lends the issue to a data- driven net-work-derived computational simulation- method also many EEG algorithmic-techniques were suggested to pinpoint the epileptic seizure onset zone as of signals data acquisitions (analog version and then conversion through digital). A number of scientific investigations both experimentally and statistical modeling for instance power spectral density within the intracranial -EEG electrode-channels comprising very higher oscillations of higher-frequencies,[9] yet the methods did not reflect and study the dynamical net-work properties of epileptic-human-brain this is due to the treating the every channel electrode EEGs separately. Whereas some others were suggested graph-theory created inferences of intra cranial electro encephalographs,[10–15] however, the procedures and methods were unsuccessful towards determining the core net-work mechanisms/properties which lead e-seizures to happen at the first instance.

Therefore, we suggest and attempt to build a biomarker for the epileptic seizure onset zone identification and also pinpointing where exactly the seizure is.

Worldwide over 65 million people (Figure 1) suffer from epilepsy and therefore, epilepsy causes seizures, seizures are hyperactive (or hyperactivity) or hyper electrical activity phenomena in the brain.[9] In the United States of America (USA) alone, over 2 million people suffering from drug resistant epileptic seizures (DRE).[16] As far as India is concerned more than > 200 million suffering.[17]

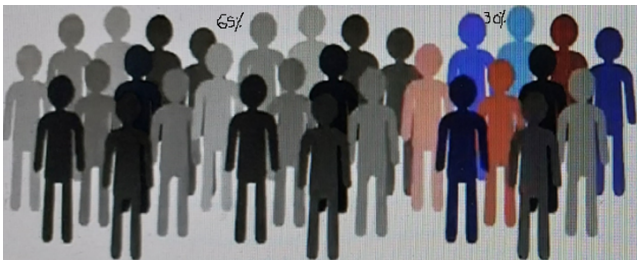

Fig. 1: World population of 65 millionepileptic seizure patients out of which 30% e-patients are shown with colors (World population of epileptic seizure patients in which 30% drug resistant, and 50% can be cured with eSoZ treatment successfully).

It might be a respite and relief and, also supportive to know understand the brain, or it could spread throughout where it is just hyper-active and synchronization and very, very synchronously which can last for 10Seconds duration. They can last for several minutes cyclically and repetitively too. However, seizures triggering (biting) is less than 0.8 milliseconds duration on the international standard scale measured so far. A subject (epileptic patient) might not even see and observe that they are having a seizure, or they might and may possibly be on the floor having fibrillations (convulsions) that are called spontaneous electrical (action) potentials, there is very variability in terms of duration and degree of severeness of any kind (or particular) of seizure. You may have been aware of epilepsy, but we cannot be so sure everyone is aware of this statistic, which is that over 30% of people who have epilepsy do not respond truly to the drugs (drug related epilepsy designated as DRE therapy). Till to date not even a single anti-epileptic medication or combination truly suppresses their seizures. And that is 30% of the population. So, you might ask, well what treatments are out there for them? Well, the usual surgical operational gold standard method is surgery. So, the idea here is that within that 30% population,[17] many of them might have what's called focal seizures or their seizures are starting in a very particular area of the brain. Now, this is a schematic diagram that showed epileptogenic zone EZ is stands for epileptogenic zone (e-Zone). This is the seizure focus, the area/region(zone) of the brain which can be triggered to trigger the seizures.[18–23]

The following Table 1 gives the patients clinical demographic details.

2. Aims and Objectives

One of 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

Table 1: Patients details

Number Patients	Total
No. of epileptic-Patients	91
Number of successors in e-patients	44
Number of failures in e-patients	47
Number of male e-patients	44
Number of female e-patients	43

epileptic patient's brain. Also, to demonstrate the seizures in between and during the attack. An attempt to develop a theory for the seizure onset zone of the epilepsy disorder.

3. Materials and Methods

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.

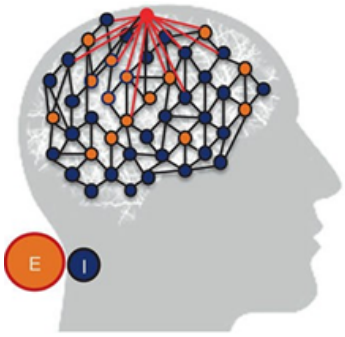

Fig. 2: A human epileptic-seizure EEG simulated model pointing the asymmetrical EEG patient (unbalanced)/epileptic-seizure excitation (E) onset zone inhibition (I).

In analog EEG, the data is generated spontaneously and dynamically with continuous (nonstop) therefore, if there any subtle changes in those analog waveforms/signals it is difficult for the clinician to pinpoint the error.

The EEG marker of SoZ, referred to as neural-delicacy or fragility (conceptually depicted in Figure 3A. and quantitatively in Figure 3B)

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.

Justification of the Figure 3: Insight of neural instability or delicacy – the upper left showing the intracranial EEG tracings amid the seizures, upper right showing while seizures 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

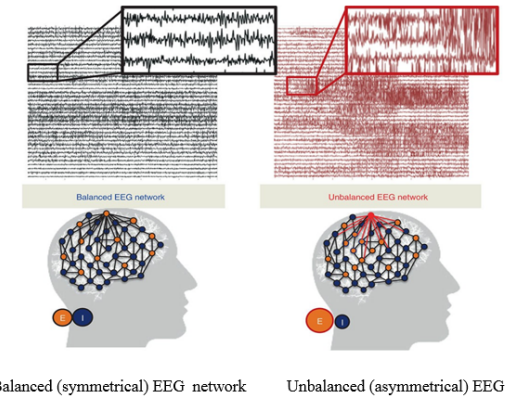

Fig. 3: Intuition of neural delicacy (fragility) - unbalanced (distorted and biased) and balanced networks.

the seizures. The entire Figure qualitatively justifying 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 $x(t + 1) = Ax\times(t)$. 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).[24,25]

4. Findings

It's usually not localized in one specific region of the brain. It might be a small NW of areas in the brain but focal means that it always starts in that same focal region and thus you can truly find it and surgically respect that tissue in hopes of stopping seizures in a patient.

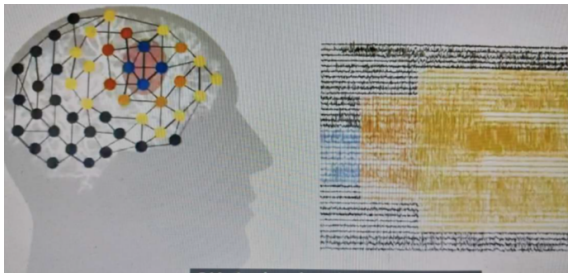

Fig. 4: The concept of source-sink rationale/hypothesis: epi-leptogenic (epilepsy genesis EG) nodes that are sources prior to e-seizures.

Consequently, this is an irreversible procedure and often surgeons will try to take out as much brain as possible without causing morbidities like impairments in perception which involves vision and speech and motion.

It's this delicate balance of take out as much as you can to make sure that the surgeons stop but to try not to impair them post op (surgery).

Now, even though that's pretty much the gold standard on average surgical success rates is 50 %. In fact, there's a variation between 30% success rate to 70% success.

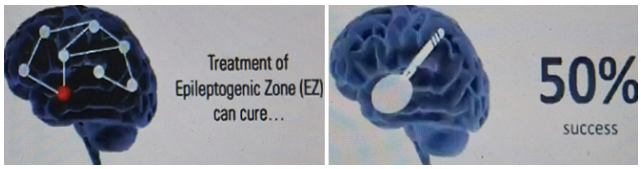

Fig. 5: Seizure zone indicated with red point

4.1. What does this mean?

That means after surgery, your seizures may return on average 50%, in 50% of the patients, which is not acceptable. This is because it's not truly trivial to find this e-zone. This analysis can be viewed in the following schematic diagram (Figure 4).

So, let's see the process of how clinicians do it in terms of what they call localizing the EG, i.e., localities of the e-SoZ or epileptogenic zone (EZ). And how we can help them using sort of systems control theory.

Firstly, when a candidate (patient) is designated as drug resistant, and they want to be potentially a surgical candidate. This is what happens. The patient goes into an epilepsy center, a specialized center that treats these types of patients and the very first thing they do is they go through a part of the screening procedure what is called, noninvasive monitoring. The following figure shows the complete picture of the surgery.

They check themselves into the hospital. They stay there for several, two weeks on average. And what happens?. Well

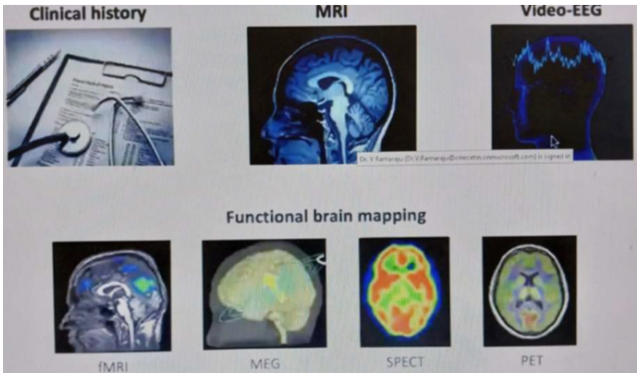

Fig. 6: Clinical history via MRI, Video-EEG,

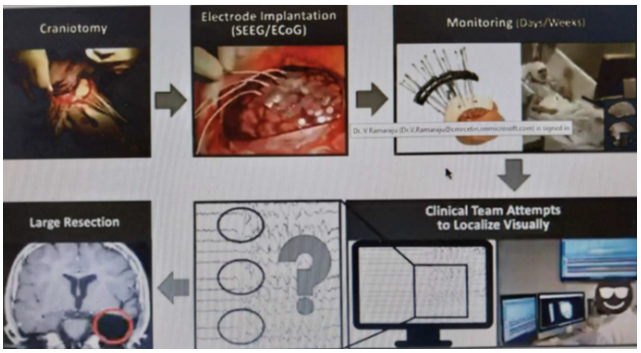

Fig. 7: A complete picture of the e-surgery

all kinds of brain imaging is done on them. They get an MRI scan because the clinicians looking to see if there is a lesion in the brain or abnormalities that might be triggering seizures and that might five them a clue as to where seizures start.

Of course they look at their clinical history. The total complete entire time what's called the EEG video which is a scalp Electrodes which are place on the surface of the patient scalp. So, it's noninvasive and the patient has the scalp EG throughout the monitoring phase they are sitting in there basically lying down in a hospital room bed for 2 weeks straight while the clinician, clinical team is waiting for them to have seizures. And what they do is they look at the scalp EEG date during seizure and say okay. We see that it's coming from the left hemisphere, we see there is more temporal frontal area so the EEG video and MRI scans. And then these are other imaging modalities that are used in some of the centers. They try to narrow down where they think seizures are starting. However technically, unless there is a lesion in the MRI, which is about 50% of the time, clinicians do not know exactly where the epileptogenic zone (e-Zone) is based on this data. They, know kind of fine (okay and good), it might be on the left hemisphere or frontal temporals. Therefore, in those case where they are not sure or unsure and they can't go straight to surgery, they do what's called invasive phase too monitoring. This

is when the patient returns, back to the hospital, stays for, again up to two weeks, several days to weeks. And this is what its invasive because what the clinicians are going to do is implant electrodes into the brain, okay. They will have to, and they must go to the surgery truly.

There is various modalities of how to invasively monitor. One is called electrocorticography E.Co.G, where you do a craniotomy, that's where they open the skull and they embed a set of electrodes on the peripheral level at the surface of (motor) cortex, that is E.Co.G here and they are more macro electrodes. Or they might go through what is referred to as stereotactic EG. Therefore, instead of doing a big craniotomy they will just drill a tiny burr hole and they will stick electrodes in each, and every hole as you see here. And therefore, smaller, and tiny holes, yet you can get more and more electrodes and you can get deep and peripheral coverage on the surface, level of the (motor) cortex. Hence, these are the two of the monitoring techniques that are invasive. The subject recovers from the surgery and they stay in the hospital room for several days to week because they want, a clinical team is just waiting for them to have seizures. And why are they waiting? This is because, they are going to inspect visually look at the EEGs on the computer system visual display monitor, prior to each, and every seizure, and, also while patient having seizures in front of the clinicians i.e., when the clinicians are present at the patient, before each, and every seizure occurrence. Here is a small example of a seizure onset. And they look to see which the channels are exhibiting some abnormal anomalous activity right before the seizure is triggered (seizures triggered). And then those channel EEGs point to the regions of the seizure zone into the epileptic patient brain that are suspected to be the epileptogenic zone or the EZ. Therefore, they do this for as many seizures as they can capture during the stay. And they form a hypothesis and say, we believe the epilepsy genesis is here and this is the surgery that we are going to perform, and they go and do the surgery. And typically, it is a larger section. Hence, that is the kind of the process. So, it is very lengthy, very detailed where a lot of data are gathered. Now, one of the things that I mentioned here is they are waiting for seizures. So that's why the patient is in the hospital for several weeks because they (then) the idea is well, how can I tell you where exactly seizures start without ever observing a seizure? So, I just want to highlight some of the limitations are here that basically and fundamentally pose the problems and then pose the problem we try to solve.

5. Discussion and Limitations

Waiting for seizures is problematical. It is high risk for the patients. The patient has their brain often exposed and there is risk for hemorrhaging and so forth. And it is very and very costly: everyday it is about five thousand American dollars (USD $5000) per day to monitor that patient. A lot of data is wasted. So, if you think of two weeks stay and a patient has say three seizures on an average (by and large) which lasts a few minutes, how much data is truly ignored? Well enormous amount of data that is when they are not having seizures, but then of course, the clinicians have no way of inspecting that data at rest and telling anybody where seizures start. Its highly subjective. Interestingly in the United States of America, there is, no analytical tools till date that process any of these data to help then find out where seizures start.

Therefore, it is often prone to human errors, relies on the expertise of the clinicians. And at the end of the day, they have a lot of uncertainty and large brain regions are resected. And of course, I mentioned that the success rates are still grim, pretty, grim. So here is question can we leverage non seizure data that is currently not being analyzed?. So, all that information? we have very rich data, electrical activity at the source, all these sources inside the brain with these types of procedures. And they are ignoring much of it because the patient is not seizing. So, the question is, how do we find the EZ when a patient is not having a seizure. Can we actually leverage that rich data? Can we find this EZ when patients are not having a seizure?

Epileptic (i.e., Epilepsy) patients are not having a seizure? So clearly, their brain is pathological. So what do you think is happening when they are not having a seizure? So, I think of the data is there is some area in the brain, this EZ that if triggered at wrong time, will generate a seizure. So, what do you thinks happening to the EZ when there is not having seizure? Any ideas? I am sure many of you thinking the right thing: what do think? So, think of it like a bomb, a ticking bomb in your brain that goes off every once a week. What do you, why would you not have a seizure all the time? So, our hypothesis and some biological evidence for it as well as, its because we believe that other brain regions as, natural protective mechanisms are inhibiting the EZ. So, there is constant inhibition trying to clamp down on that EZ 24/7. And for whatever the reason, may be its fatigue, may be, it's a fluke or a specific stimulus that sort of reduces that level of inhibition that could allow the seizure to occur, to happen, but its inhibition. And this is our bodies way of protecting ourselves from that damage. Right? So, I want to present seizures. Therefore, it makes sense to hijack other brain regions to say now your functions is to just inhibit this area. Okay, so, we are going to think about that idea and say, okay, if that is the case, then I should be able, to from these data, this intracranial EEG data, I should be able to find two types of brain areas, one area or a group of nodes that we being inhibited constantly being inhibited in terms of their network that are inhibiting, doing the inhibiting. Okay, so we are going to talk about these as sinks and these as sources, and we are going to talk how, we use the data to find out that, Okay. So, some definitions (just like that).

6. 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 resect can be done accordingly. The source is the 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 a complex yet nebulous neural-net-work, in which the nodes are connections, and various regions or it can be within the areas (zones) and the weights are the network branch edges (between node to node connection) that dynamically influence within the second in e-patients. Thus, the source in the e-brain‘s neural-nets are within the sink only.

7. Conflicts of Interest

All contributing authors declare no conflicts of interest.

8. Source of Funding

None.

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Author biography

V Rama Raju, Professor

V Malsoru, Associate Professor of IT

K Srinivas, Professor & Head

B. Kavitha Rani, Professor & Head

G Madhukar, Associate Professor

Cite this article: Raju VR, Malsoru V, Srinivas K, Rani BK, Madhukar G. Seizure epilepsy genesis and epileptogenic nodes in epileptic patients: A procedure. *IP Indian J Neurosci* 2022;8(4):248-253.