Original Research Article

Neural instability and delicacy while the electro-encephalography indicator of epileptic seizure (e-seizure) on set zone

V Rama Raju^{1,2,3,*}¹CMR College of Engineering & Technology, Medchal Road, Kandlakoya, Hyderabad, Telangana, India²Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India³CMR Institute of Medical Sciences, Medchal Road, Kandlakoya, Hyderabad, Telangana, India

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ABSTRACT

More than 15 million seizure-epileptic subjects (patients) do not respond to medication globally. Surgery necessitates thorough elimination or separation of the epileptic-seizure onset zone (ESoZ), regions of epileptic brains where seizures derive (come from). Sadly, the success rates of operation differ amongst 32% and 72% and this is due to clinically and hence prognostically no authenticated or substantiated (i.e., corroborated) biological or physiological indicator of the ESoZ exists. We discuss, as well as confirm a new electro encephalography indication neural vulnerability in a retroactive study of 90 subjects (patients) by applying neural instability of the interpreted ESoZ as a metrical to expect operational (invasive) results in retrospect (retrospectively). Susceptibility expects (43/47) surgical (invasive)-failures, as well as a total likelihood precision of 76% assessed through the precision of neuroscientists at 48% (positive-results).

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1. Introduction

Around fifteen (15) million epileptic-seizure (e-seizure) subjects (patients) are suffering and do not respond to medications globally and more than 1million in America grieve from drug resistant epilepsy (DRE).^{1,2} The DRE is demarcated as continued seizures despite two trials of appropriately chosen anti-epileptic drugs.³ Subjects with DRE come up with an enhanced hazard of abrupt and unexpected demise/passing besides they are often hospitalized and hampered thru epileptic-seizure-associated infirmities plus the cost-of-care (CoC) is very-substantial.⁴ Circa, 51% of epileptic-patients with DRE have focal DRE, where particular brain area(s), characterized or designated as the seizure-epileptogenic zone (SEZ), is crucial and necessary for instigating the epileptic-seizures and seizures elimination (or discontinuation/or stoppage) results in the

whole obliteration/or-abolition of the epileptic-seizures.^{5,6} The SEZ encompasses the diagnostically hence clinically-too discovered ESoZ and in advance spread-zone and/or transmission-zone.

2. Materials and Methods

The anatomical-brain zones coupled through the ESoZ determine the most basic and quickest electro physiological variations in the course of the for the duration of the epileptic-seizure-event then normally herald the clinical/ and/or diagnostic-onset of the seizures. Furthermore, the experimental (early on) spread-zone-regions (SZRs) are implicated at the time of the most primitive experimental (semio-logical) feature-manifestations throughout the epileptic-seizure-event. Effective surgical-operation plus neuromodulatory therapies can avoid and prevent e-seizures totally or let them to be monitored and/or regulated through medications,⁷ however results for both therapies/treatments

* Corresponding author.

E-mail address: drvrr@cmrcet.ac.in (V. R. Raju).

critically/significantly vary on precise pinpoint of the ESoZ.

Focusing the locus or pin point of the ESoZ additionally depend on the perfect position of the sensors, i.e., electrodes such that they cover up the SSoZ plus the capability to distinguish deformities or malformations in the intra cranial electro encephalography, i.e., iEEG/(i-EEG) channels that might connect to the ESoZ through the nude-eye. Regrettably, and hence sadly, even the highly skilled clinicians are confronted for the reason that epileptic-seizures is profoundly a net-work-disease (NWD), that cannot be completely characterized with the existing procedures and techniques of localizing the eSoZs. Irregular networks around various sensory-channels might signify a further efficient indicator of the ESoZ.⁸

And thus, the locus-of-focus or focus-of-localization lends the problem/ the subject-itself to a data-driven network-based computational approach, plus numerous electro encephalography (EEG) algorithmic-techniques and modules have been proposed/suggested to identify, to pinpoint the SSoZ from the epileptic-seizure EEG signal acquisitions/recordings. Several involve studies of the power-spectral-density(PSD) in every i-EEG-channel, together with elevated-frequency fluctuations or vacillations/ or oscillations(HFOs).⁹

However these methodologies do not contemplate or reflect the net-work properties of the human anatomical-brain cause they extravagance every i-EEG channel autonomously or individualistically. Others have suggested non-linear graph-based analyses of i-EEG data.^{10–14} however these methods give way and go wrong to detect core basic-net-work properties which trigger e-seizures to appear in the earliest-area-point.

So, we aim, we suggest an E.E.G-indicator of the ESoZ, which we call neural subtlety or abstractly depicted in Figure.1, A and B and quantitatively. To create the instability or vulnerability indicator, we initially and originally develop a customized dynamical-model-simulation or a prototype of the anatomical-brain network as of (from) examined i-EEG-waveforms/signals, Figure.1, shown in/at upper-row. The reproductive model-prototype be able to precisely modernize and restructure the i-EEG signal-acquisitions/recordings from two patients.¹⁴ Then, we determined neural instability, which determines the degree/or intensity to which net-work nodes are asymmetrical-imbalanced/or extreme, i.e., tiny, and modest impulse (pulse) distresses(perturbations) on the net-work and therefore can trigger seizures, see the Figure 1A, and B.

In Figure 1 A, The i-EEG traces amid left e-seizures then through a right e-seizures. In Figure 1B, net-work representation displaying variations (asymmetrical signals) in right connectivity in a delicate node which bases e-seizures. Qualitatively, which labels the notion of neural-insubstantiality in the milieu of active—dynamic i-EEG

net-work, through nodes demonstrating and signifying excitatory depicted with “E” and inhibitory with “I” neural-populations (“populations-of-neurons”).

From an active- dynamic-systems perspective, such disparity ascends /or rises from a limited brittle nodes instigating variability or unpredictability of the net-work in the form of over excitation, or under inhibition. We delineate delicacy of a net-work node to be the least vitality trepidations smeared to the weights of the node on its neighbors beforehand interpreting the net-work unstable.

In control and systems theory (system identification), stable-systems yield to a base-line state once a node is disconcerted. In disparity, unstable-systems can fluctuate/oscillate besides raise once a node is distressed. In the setting of perspective of e-seizure, a brittle node is one that necessitates a slighter disconcertion to lead to e-seizure activity-movement. Instability system can be demonstrated in the perspective of linear-dynamical-systems, like $x(t+1)=Ax(t)$. Disturbing the columns of the matrix-A shall vary lively-dynamic-connections of a specific-node, i.e., that column on-its-neighbors, ensuing in a biased net-work.

To assess neural-insubstantiality as an indicator for the E.S.o.Z, we demonstrated a reviewing study by employing i-E.E.G. data from 90 subjects healed.

All the subjects with D.R.E underwent invasive i-E.E.G. checking followed by operational (invasive)-resection or optical maser (laser) excision(removal/ablation) of the E.S.O.Z. success rate was partially 50% to 50% (success in44/90; unsuccess/failure-results (outcomes)) in 46/90. We demonstrate that neural-instability is greater (smaller) in cathode-contacts inside scientifically marked ESOZs for e-seizure-subjects in conjunction with a effective/positive (unsuccessful) results (outcome). Furthermore, we evaluated delicacy of i-E.E.G. nodes to 6frequency-based plus14 grid (connected-graph) hypothetical-characteristics(feature-manifestations) in a 10fold nestled cross-validation-(C.V.) experimentation. Neural-vulnerability has an area-under-curve (AUC) differential score-of 0.89 ± 0.065 , which is circa~13% improved-than the following most-best-feature. Moreover, it has a superior level-of-interpretability, which we demonstrate by computing an interpretability-ratio. At the same time, mutually, the findings imply that temporal-spatio-temporal heat-maps of neural-instability might be a health vigorous i-E.E.G-biomarker of the E.S.O.Z in addition to it can be impeccably unified into the clinical/scientific system-work-flow.

3. Findings

Scientifically there is no validated bio marker of the ESOZ, however it is an essential element for the locus of the fundamental and inherent epilepticus s-zone. This introduces a significant experiment for neuroscientists (neurosurgeons, neurologists) to precisely pinpoint the

Fig. 1: Perception of neural-instability— left-side symmetrical (stable) and right-side asymmetrical(unstable) net-works.

ESOZ and has led-to operational (invasive)surgical-success-rates to differ between 30% plus 70% regardless of substantial-brain-areas being-eliminated. In conjunction with no bio marker existing, the neurophysiologists and surgeons perform wide-ranging assessments through the high Tesla functional neuro imaging, clinical-experimental-examination/testing and optical/visual-examination of electro encephalography (E.E.G) signal-recordings.

While non invasive tests are in conclusive, subjects undergo intra cranial examining, whereby i-E.E.G electrodes are implanted into the e-seizure-subjects-brain. i.E.E.G gives superior spatio-temporal-resolutions (dynamic-ranges), data for neuroscientists to visually-distinguish asynchronous, i.e., abnormal-activity, for example spikes plus superior-frequency-bursts (more oscillations with noise and distortions), in the middle-of e-seizures(interictal) as well as in the course-of-seizures(ictal), can be an outline in Supplementary Figs. 1 and 2). Specifically, clinicians attempt to identify electrodes involved in the E.S.O.Z and also early on before-time-spread. Without the area- intersects/ or-overlaps through the articulate-cortex, operational(invasive)surgical-resection is then accomplished on the basis of this hypothesis.

We analyzed iEEG data from every patient using instability and 20 other baseline features, which resulted in spatiotemporal heatmaps for every feature. The baseline features included spectral power in various frequency bands (for example, delta band 1–4 Hz) and specific graph measures of bivariate correlation measures (for example, eigenvector centrality and degree of correlation and coherence matrices), which have been previously reported in the literature to correlate to the SOZ10–13. We evaluated each feature by predicting surgical outcomes (process outlined in Extended Data Fig. 1).

Neural-tenderness is a model-shift in the electro encephalography (E.E.G) analytics-area which is a notion based on the assumption or inference that focal-seizures(f-seizures, or e-focal-seizures) ascend or rise from a limited delicate or brittle-nodes (i.e., the ESOZ), that provides the cortical-e-seizure net-work on the verge of instability. While one examines the i-E.E.G-data in the course of interictal/or-preictal, cycles, action-movement taped, i.e., acquired from every-electrode-channel seems to float across a zero-line, i.e., electrical-base-line value (Figure. 1). If the network is 'symmetrical', then it will transiently respond to an impulse but always returns to a baseline value.

Organically, unevenness as a result of trepidations amid excitative and repressive connections of a neural-net-work will happen over some number-of-mechanisms, for instance preeminent-glutamate, a genetic-syndrome distressing synaptic-hang-up/or reserve, declined and diminished-GABA-receptors, enclosure-of axo-axonic gap-connections/intersections, loss-of-inhibitory(L.o.I) chandelier-cells or axonal-developing/germination from layer-V excitative pyramidal/or pyramidal-cells. This disparity/asymmetrical-imbalance within a neural-net-work might produce functional-instability, where by, electrical-impulses at a variety of nodes result in frequent recurrent-seizures. While i-E.E.G cannot-differentiate amongst excitative and repressive neuronal-populations, the notion of asymmetrical(unbalanced) disparity affecting the net-work to be on the verge-of-instability (VoI) will be developed by neuronal/(neural) vulnerability at the i-E.E.G net-work-system-level.

To determine in what way instability is processed from a dynamical-model, we consider/care-about a two-node net-work. A balanced-steady net-work-system is shown in which fervor and reserve are symmetrical(unbalanced/or imbalanced). The net-work-model in the upper-row as well as does a line a r f o r m, of $x(t+1)=Ax(t)$, somewhere 't' is a time-index, usually 1milliSec.

However, less than 8 milliSeconds the seizure-occurrence (duration) on the international scale. Even though the repressive node is induced stimulus through an instinct and impetus, both-the-nodes momentarily react plus the E.E.G signal recordings coming back to the electrical-baseline, i.e., zero(0) line.

4. Conclusions

Latest in scientific-advances developing from neural-vulnerability. Neural-instability has the potential to redefine in what manner and by what means epilepsy surgery is performed, departing from the classical localization paradigms and en bloc resections to a personalized network-based user-friendly visualization and surgical strategy. By developing a three-dimensional (brain region, time and instability) network-based method for anatomical representation of the epileptiform activity, including the seizure onset areas and the early propagation zone, this study will have the potential to offer a safer, more efficient and cost-effective treatment option for a highly challenging group of patients with disabling DRE. More precise SOZ localization using neural instability would also guide chronic implantation of neurostimulation devices aimed at suppressing seizures with bursts of current when detected.

Neural instability may also be relevant in detecting epileptogenic regions in the brain when applied to interictal (between seizures) i-EEG recordings. Seizure i-EEG data are currently the gold standard in clinical practice for localizing the ESOZ.

However, having patients with electrodes implanted for long periods of time, and requiring the monitoring of multiple seizure events over many weeks, carries the risk of infection, sudden death, trauma and cognitive deficits from having repeated seizures. This contributes to the large cost of epilepsy monitoring. If a candidate i-EEG marker could be found that is able to provide strong localizing evidence using only interictal data, then it would substantially reduce invasive monitoring time. Neural instability is an EEG marker that can also further advance our knowledge of neural mechanisms of seizure generation that will then drive more effective interventions. For example, instability can be used to identify pathological tissue that is then removed and tested in vitro for abnormal histopathological structure.

Knowledge of structural abnormalities may inform new targeted drug treatments. In the future, specific instability patterns can be correlated with specific pathological substrates. Likely, the specific pathological substrates will have different therapeutic approaches. As an example, epilepsy caused by focal cortical dysplasia is treated with focal surgical resection, but post-encephalitic epilepsy may have a better therapeutic response with immunosuppressants and steroids.

Finally, neural instability may have broader implications in understanding how underlying brain network dynamics change during intervention (for example, with drugs or electrical stimulation).

Instability analysis can be applied as a method of assessing the efficacy of specific drug trials to specific pathological groups, which include not only epilepsy but other neurological conditions such as Alzheimer's disease or the spectrum of dementias. Commonly, the current optimal criteria to recognize therapeutic success in many neurological conditions are purely clinical, but clinical responses are not immediate. This delay in recognizing the appropriate drug and adequate therapeutic doses is highly detrimental.

Computational methods such as instability measuring EEG before and after drug administration could provide additional criteria for drug responses.

This quantitative measurement can be immediate, guiding the treating physician to the correct treatment without delays and unnecessary drug trials. Furthermore, if neural instability could be accurately obtained from noninvasive tests or from permanently implanted devices, the current instability of the network could be used as a surrogate marker of the current clinical state of the patient. As such, the changes in instability could be used as a proxy for improvement or recurrences that occur as medication doses (or other treatments, such as the keto diet⁵⁰) are changed over time.

5. Conflict of Interest

The authors declare that there is no conflict of interest.

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None.

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Author biography

V Rama Raju, Professor

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