THE TELL-TALE OVERTONES OF DEEP BRAIN STIMULATION IN EPILEPSY AS EVINCED THROUGH DYNAMIC TOOL OF HEART RATE VARIABILITY (HRV): A NEW BEGINNING IN EPILEPSY MANAGEMENT PROTOCOL

Amitabh Dube,
Professor, Physiology, S.M.S. Medical College and Attached Hospitals, Jaipur-302004. India.
email id: ***amitabhdube786@gmail.com***

Epilepsy (the Greek verb derived from *epilambanein*meaning *to take seize, take hold of or attack*) is a chronic non-communicable disorder of central nervous system that is best described by neural architectonics (Fingelkurts and Fingelkurts, 2004) as an unprecedented *avalanche of distributed neural connectomic networks firing in phase and in synchrony* giving rise to the symptom-complex of epilepsy. The distributed neural circuitry network behaviour fires primally in synchrony evolving into *seizure generation* resulting from *nodal, pathway, nodal and pathway* and *emergent*deviants (Gummadavelli et al, 2018). The presence of dysfunctional neural network circuitry dynamics with overwhelming changes in dynamical neural connectivity and network weights measures evolving through large-scale network epileptogenesis with widespread manifestation of interictal phenomena of *EEG spiking* and *high frequency oscillations (HFOs)* have been documented by real-time studies of *intracranial electroencephalography (icEEG), scalp EEG, functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG)* doing the interictal period (Frei et al, 2010; Constable et al, 2013; Sinha et al, 2017). Such studies have validated the presence of such a wide-scaled *seizure generating neuronal network pool*, documented and verified mesocscopically through the neural imaging measures in real-time.

Zaveri et al (2010) have documented a cascade flow of *neural network circuitry failure* with primal involvement of *thalamus and cortex* that subsequently concludes into the *neuronal avalanche of uninterrupted and unabated synchronous apoplectic and spasmodic neural firing*. Additionally, the *on-centre/off surround and off-centre/on surround betrothed neuronal pools as evinced through the respective intertwined and closely looped wave-frequency pattern of event-related synchrony (ERS) and event-related desynchrony (ERD) of the network circuitry* during a functional stimulus-adequate response [seems to be disrupted and hijacked by the paroxysmal neural circuitry firing. The neural network processing is primarily based on*memory formation and information flow* being represented through neural network processing of *event-related synchrony (ERS) and event-related desynchrony (ERD)* that fine-tune neural dynamical output (Dube et al, 2021) and such a structured and patterned networking profile disrupts into the synchronous avalanche of unabated convulsive neural firing.

This appreciation of the documentation that *epilepsy* is primarily consequent to *aberrant neural network architectonics* initiated the genesis of new avenues for diagnostic, therapeutic and preventive regimen protocols expanding the horizons for devices that tend to reorient and re-wire the aberrant and deviant *neural network circuitry* resulting in a decrease in frequency and intensity of paroxysmal seizures with consequent shut-down of the nervous system. Such a paradigmatic change in appreciation of pathophysiology and the antecedent therapeutics of *epilepsy* opened portals for *neuromodulatory deep brain stimulatory devices* that generate and fire electrical impulses in a frequency range over and above the maximal firing frequency range of *human mind* inducing an *electrical milieu of daze and freeze (a phase of electrical quiescence)* of ongoing reverberatory neuronal paroxysmal avalanche leading to reversal to inherent *asynchronous stochastic trajectorial electrical rhythm of the normal healthy human mind* [*virtual stochastic trajectorial phase-space* of Dube (2011)] and such devices are principled on a *chronic open-looped system* or *a responsive closed-looped system* targeting *seizure onset and* *generation zones inclusive of major nodes within the identifiable neural network circuitry*.

The management protocol of epilepsy witnessed an evolving archetypal change in terms of *Deep Brain Stimulation (DBS)* with centred weightage on select neural network circuitry inclusive of *thalamo-cortical network, the hippocampal-amygdaloid-hypaothalamic circuitry, frontal-parietal and occipital-temporal neural architectonics* (Gummadavelli, et al, 2018). As of present times, varied *thalamic nuclei (anterior, centromedian-parafasicular, centrolateral and intra-laminar nuclei) with seizure generation network* have been targeted with *network stimulation* and *responsive neurostimulation* for treatment of refractory epilepsy. The *thalamus*, *information processing hub (with anterior nucleus representing extended hippocampal system along with papez circuit*), has a primal cardinal role in network priming and igniting the *neuronal synchronous avalanche* and algorithmic modulatory nodal neurostimulation of *anterior nucleus of thalamus* within the *papez neural circuitry* tends to initiate desynchrony and recalibrate the recruited neuronal network.

The article of Lőrincz et al (2022) on influence of *anterior thalamic nucleus deep brain stimulation on dynamic patterning of sympatho-vagal interplay as evinced through Heart Rate Variability (HRV)* documents an *HRV pattern of enhanced vagal influence i.e., increased HRV metrics* subsequent to *DBS* in patients with refractory epilepsy as documented through the linear correlates of *HRV (time and frequency domain variables)* further corroborates the re-orienting, re-wiring and plastic influence of such a *DBS therapeutic modality* that has the potential to give beneficial effects in such candidate epileptic patients who are refractory to management. *Heart Rate Variability (HRV)*epitomises alternating and transforming inter-beat time intervals of a *healthy heart (a non-metronome)* and such oscillatory patterned qualia cataloguing *neuro-cardiac functions* is consequent to the intricate evolving *sympatho-vagal non-linear neural network dynamical interplay* (Goldberger, 1991). The *HRV metrics* is quantified along *time domain indices* exemplifying *HRV premise* assessed during the monitoring period (of 2 minutes to 24 hours), *frequency domain parameters*characterising absolute or relative amount of signal energy within respective component bands with *non-linear variables inventories* evaluating unpredictable complexes of time-series of inter-beat intervals (The Task Force Report, 1996). The *sympatho-vagal non-linear neural network dynamical interplay*, as indexed by *HRV,* qualifies emergent interdependent neural network dynamics operating on evolving coordinates of space and time and quantifies homeostatic neural mechanisms that adapt to *changing internal and external milieu* representative of an asynchronous neural dynamical system (Beckers et al, 2006; Dube et al, 2001). *HRV metrics* representing *sympatho-vagal non-linear neural network dynamical interplay* have the potential toquantify neural network profile with *decreased and dysfunctional HRV metrics* in epileptics (Lőrincz et al, 2022) plausibly predicting an impeding ictal neural paroxysm.

Such a finding of Lőrincz et al (2022), documented and supported by similar observations from other centres, could open new chapter in therapeutic management protocol of patients of refractory epilepsy with a closed-loop neuromodulatory deep brain stimulation that is closely synced and looped onto the dynamical HRV metrics, with a falling HRV providing the trigger to initiate the algorithm-driven stimulatory neuromodulation with the consequent amelioration of intensity and frequency of paroxysmal epileptic seizure (Piper et al, 2022).

Conflict of Interest

There is no conflict of interest with no funding source for the above editorial on the associative phenomenon of *Heart Rate Variability (HRV)* and *Electroencephalographic (EEG) signals*, consequent to ongoing work on *Biological Signal Processing (BSP)* that was initiated way back in 2003 in health and varied disease forms, respectively and is original in nature and author's sole appreciation of underlying non-linear neural dynamics of *HRV* and *EEG signals*. It has been ensured that the submission bears no semblance of fiction and/or infringement on someone else's work and is a result of appreciation of primal dynamical phenomena of *chaos of cosmos*.

Acknowledgement

The journey along the fascinating frontiers of *Biological Signal Processing (BSP)* had been and is still being guided and driven by *the esoteric force of* **LatePadma Shri Professor (Dr.) Ashok Panagariya**, who is instrumental is driving the ongoing work to its logical conclusion.

References

1. *Beckers F, Verheyden B, Aubert AE. 2006. Ageing and nonlinear heart rate control in a healthy population*. Am J Physiol Hear Circ Physiol, 290, H 2560-70.

2. Constable RT, Scheinost D, Finn ES, Shen X, Hampson M, Winstanley FS, et al. 2013. *Potential use and challenges of functional connectivity mapping in intractable epilepsy*. Front. Neurol. 4, 39.

3. Dube A. 2011. *Neural Dynamics and Human Consciousness: A Tryst with Destiny, pg 1-29*. Lambert Academic Publishing, Germany.

4. Dube A, Kumar U, Gupta K, Gupta J, Patel B, Singhal SK, Yadav K, Jetaji L and Dube S. 2021. *Language as the Working Model of Human Mind. Book, Brain-Computer Interface. IntechOpenPublishsing, 3-22*.

5. Goldberger AI. 1991. *is the normal heartbeat chaotic or homeostatic*? News Physiol Sci, 6, 87-91.

6. Fingelkurts A and Fingelkurts A. 2004. making complexity simpler: multi variability and metastability in the Brian. International Journal of Neuroscience, 114 (7), 843-862.

7. Frei MG, Zaveri HP, Arthurs S, Bergey GK, Jouny CC, Lehnertz K, et al. 2010. *Controversies in epilepsy: debates held during Fourth International Workshop on seizure prediction*. Epilepsy Behav, 19, 4-16.

8. Gummadavelli A, Zaveri HP, Spencer DD, Gerrard JL. 2018. *Expanding Brain-Computer Interfaces for controlling epilepsy networks: novel thalamic responsive neurostimulation in refractory epilepsy*. Frontiers in Neuroscience, 12 (474), 1-13

9. Lőrincz Nora K, Balas I, Halasz, Bela F, BónéB, Kis-Jakab G, Tóth N, et al. 2022. *effects of anterior thalamic nucleus deep brain stimulation on interictal heart rate variability in refractory epilepsy patient*. Clin. Neurophysiol. (In print)]

10. Piper RJ, Richardson RM, Worrell G, Carmichael DW, Baldeweg T, Litt B, Denison T and Tisdall MM. 2022. *Towards network-guided neuromodulation for epilepsy*. Brain, 145, 3347-3362.

11. Sinha N, Dauwes J, Kaiser M, Cash SS, Brandon Westover M, Wang Y et al. 2017. *Predicting neurological outcomes in focal epilepsy patients using computational modelling*. Brain, 140, 319-322.

12. The Task Force Report. 1996. *heart rate variability: standards of measurement, physiological interpretations and clinical use*. Circulation, 93, 1043-65.

13. Zaveri HP, Pincus SM, Goncharovali, Novotny EJ, Duckrow RB, et al. 2010. *Background intracranial EG spectral changes with anti-epileptic drug taper*. Clin. Neurophysiol., 12, 311-317.