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Mini Review

Seizure Suppression Using Low-Frequency Stimulation to Connectomics: New Directions to Epilepsy Therapy

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Epilepsy is a neurological syndrome where there is an abnormal, spontaneous, excessive, repetitive, synchronous firing of groups of neurons and affects 1-2% of the world population [1]. It does not follow any geographic barriers, gender, race or age-preferences [1]. It does however show a tendency to peak at early and later years of life [2]. Mankind has known it for centuries [3]. According to the International League Against Epilepsy classification of epilepsy, there are at least fifty sub-types of epilepsies [4].

Although, about 75% of epilepsies are treatable and controlled with conventional medications the remaining 25% are difficult to treat [1]. In the latter patients alternative therapies are required. In about half of these patients, surgery is attempted [5]. For the remaining half, surgery is not possible either due to the critical anatomical location of the seizure focus or the nature of epilepsy [5]. Thus, in almost 10% of this epileptic patient-population the seizures are refractory and yet we do not have any effective therapeutic intervention.

Ictogenesis and epileptogenesis

Despite decades of relentless, extensive scientific research we do not have a definitive unified understanding about the ictogenesis and epileptogenesis. Perhaps, there is no unified answer either for a heterogeneous phenomenon such as epilepsy. Studies have ranged from drosophila [6] to the mammals [7]; *in vitro* single cell and gene-expression [8] and slice studies and optogenetics [9] to human patients [10-12] and more recently, neural network computational modeling [13]. The explanation for an abnormally excitable brain responsible for seizures and epilepsy could be residing anywhere along the cascade of disturbed ionic milieu [14], an imbalance in excitatory-inhibitory neurotransmitter interaction [15], synaptic plasticity [16], glia-neuron disturbance [17] to a hyperactive kindled neural-network [18].

A parallel and an exponential increase in the tools of investigations in neuroscience such as neuroimaging, electroencephalography (EEG) [19], magnetoencephalography (MEG) [20], single-cell recording and patch clamp [21] genetic manipulations and knock-out strategies [22] to name a few has made this journey of exploration not only exciting but also equally challenging. Sometimes one wonders; are we "missing the forest going thus close to the tree"?

Seizures beget seizures and the kindling phenomenon

Across all species, neurons particularly in the forebrain areas demonstrate a characteristic progressive, enduring pattern of firing on repeated stimulation that is called "Kindling" [23]. Furthermore, in epileptic patients first unprovoked seizure has 30% chance and a second one has a 75% chance of recurring [24]. Thus, seizures seem to beget seizures. This nature of seizures and epileptic neural network quite often getting trapped into a relentless progression requires early and appropriate medical attention. Moreover, the kindled network could, like a wild forest fire, invade into other areas of the brain and thus compromise functions such as cognition and emotions as well [25].

Unfortunately, as many as 10% of the epilepsies are refractory to conventional medical treatment and are not even accessible to surgical interventions [5]. Alternative therapeutic approaches are therefore necessary. Extensive scientific research is in progress towards that end.

Seizure control at the level of neural network

Although most antiepileptic medications might be suppressing the epileptic seizures at the level of ion-channels, membrane dynamics or neurotransmitter interactions [26] they might not be effectively controlling the hyper-excitable brain at the level of its network.

As an offshoot of investigations such as EEG [19], functional neuroimaging [20], diffusion-tensor imaging [27], computational models of neural network, EEG signal processing algorithms and graph theory a relatively new approach has emerged to analyze the dynamics of a normal as well as an abnormally operating neural network [28]. This data could in turn be used in developing alternative non-conventional techniques for seizure suppression when the conventional therapy fails and seizures have become relentlessly progressive. The philosophy of such an approach relies on the concepts of synchrony and desynchrony of neural network [29].

A putative pool or "focus" of neurons such as hippocampus or amygdala in the temporal lobe could be trapped into firing in an abnormal hypersynchronous mode [29]. This in turn could drive other neighboring networks and thereby increase the connectivity of the network [30]. Such a high frequency, hypersynchronous network could be reverted back to fire at a frequency determined by an external electrical pulse [31]. The ideal frequency suitable for such an entrainment of frequencies is typically in the lower bandwidth of 0.5-5 Hz [32].

Deep-brain low-frequency stimulation (LFS) and seizure suppression and the phenomenon of "Quenching":

In rat models kindled seizures and the accompanying electrical after-discharges have been shown to be effectively suppressed using repeated low-frequency sub-threshold electrical pulses [33]. In a separate study, we investigated the kindling and seizure suppressing effect of single low-frequency stimulations in the hippocampus and amygdala in both the early and late stages of epileptogenesis [34].

Over the past two decades several other studies have confirmed similar seizure suppression phenomena particularly with LFS using more extensive multi-electrode recordings, micro-positron-emission tomogram [32] and tools in molecular biology [35]. Such studies have provided a deeper understanding of the mechanism underlying the effect of LFS.

The mechanism of seizure suppression particularly brought about with LFS has also been explained based on the "Quenching" phenomenon used to characterize long-term-depression (LTD) in the *in vitro* slices caused by low-frequency pulses [36].

Low-frequency seizure suppression from laboratory animals to the humans:

Lessons learned through animal experimentation are already being translated into treating human epileptic patients [29]. Electrical stimulation of brain tissue as well as peripheral nerves [37] to treat intractable epilepsy has been practiced for quite some time. Vagal stimulation protocols have been approved by the U.S. Food and Drug Administration (FDA) and world wise [37].

Deep brain stimulation protocols using pulses of different frequencies determined by the target area of interest are being established. Although the most common frequencies that have been reported to successfully suppress limbic as well as cortical seizures are in the low-frequency band width of 0.5-5 Hz., some other related studies indicate that higher frequencies of 60-185 Hz are better at seizure suppression and in fact, lower frequencies could be detrimental to control the seizures. But the targeted areas for such phenomena were different. Moreover, with frequencies in such higher range there is always a great concern of increased predisposition to provocation of seizures subsequently [29].

Neural prostheses are being constantly designed for treating seizures in patients that are refractory to conventional treatments [29]. Besides the parameter of frequencies of the pulse, other characteristics such as the amplitude, duration, varying predetermined stimulus intervals etc. are also being considered [38]. For instance, periodic LFS pulses given at fixed predetermined frequencies to various areas in the temporal cortex including amygdala have been considered less beneficial and in fact at times epileptogenic compared to more effective closed-loop devices that provide non-periodic LFS just prior to the seizure as determined by the EEG signals [29]. In fact, such a responsive neurostimulator from Neuropace has been granted approval for use in patients' refractory to antiepileptic treatment by the FDA [39]. Moreover, such closed-loop non-periodic stimuli have lower risks of local tissue damage due to the electrode implant [39].

Trans magnetic stimulation (TMS) to suppress seizures is yet another mode of rendering the seizure suppressing LFS that is being widely reported [40]. In fact, there seems to be an encouraging evidence of successful seizure control with TMS even with the most relentless, devastating seizures that accompany Rasmussen's encephalitis [41].

Connectomics and signature patterns of neural networks

The rate of kindling varies across species animals and between subjects [42]. In our studies with computational neural network modeling of kindling and epilepsy we have found that altering the number of neurons in the network significantly determines the rate of kindling [43].

As stated earlier, it is even more intriguing to know that the seizure suppression effect of LFS is not universal to all the brain areas. Some regions respond more effectively to HFS than with LFS [29]. This is not surprising as the inherent frequency of each cluster of neurons could be different.

A relatively new field namely, "Connectomics" helps us analyze the connectivity of neuronal pools in a dynamic brain network that is constantly changing under the destabilizing influences such as epilepsy [44]. Connectomics incorporates the data from techniques such as MRI-tractography, fMRI, EEG and graph theory analysis from the epileptic patients [45].

The basic premise of Connectomics is that the dynamics of a neural network is determined not just by the pools of neurons that are connected but, by the nature of their connections. Although this principle of Connectomics seems logically obvious and straight- forward it was not possible to investigate the diverse connections between neurons until recent times when high resolution neuroimaging and tools of computation and analysis such as graph theory merged [46].

Thus, neurosurgeons are getting better at predicting the outcome of their temporal lobe surgeries for epilepsy by analyzing the connectomic data of their patients beforehand [45].

What is equally if not more fulfilling is that combining LFS with functional imaging of brain connections in patients with refractory epilepsy allows us to constantly monitor the changes in the brain network as the therapy is being offered [44,45].

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