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Review

Epilepsy as a dynamical system, a most needed paradigm shift in epileptology

Márcio Flávio Dutra Moraes [a,b,*], Daniel de Castro Medeiros [a], Flávio Afonso Gonçalves Mourao [a,b], Sergio Augusto Vieira Cancado [c], Vinicius Rosa Cota [d]

[a] Núcleo de Neurociências, Departamento de Fisiologia e Biofísica, Instituto de Ciências Biológicas, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil
[b] Centro de Tecnologia e Pesquisa em Magneto Ressonância, Programa de Pós-Graduação em Engenharia Elétrica, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil
[c] Núcleo Avancado de Tratamento das Epilepsias, Hospital Felicio Rocho/Fundação Felice Rosso, Belo Horizonte, Brazil
[d] Laboratório Interdisciplinar de Neuroengenharia e Neurociências, Departamento de Engenharia Elétrica, Universidade Federal de São João Del-Rei, São João Del-Rei, Brazil

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ABSTRACT

The idea of the epileptic brain being highly excitable and facilitated to synchronic activity has guided pharmacological treatment since the early twentieth century. Although tackling epilepsy's seizure-prone feature, by tonically modifying overall circuit excitability and/or connectivity, the last 50 years of drug development has not seen a substantial improvement in seizure suppression of refractory epilepsies. This review presents a new conceptual framework for epilepsy in which the temporal dynamics of the disease plays a more critical role in both its understanding and therapeutic strategies. The repetitive epileptiform pattern (characteristic during ictal activity) and other well-defined electrographic signatures (i.e., present during the interictal period) are discussed in terms of the sequential activation of the circuit motifs. Lessons learned from the physiological activation of neural circuitry are used to further corroborate the argument and explore the transition from proper function to a state of instability. Furthermore, the review explores how interfering in the temporally dependent abnormal connectivity between circuits may work as a therapeutic approach. We also review the use of probing stimulation to access network connectivity and evaluate its power to determine transitional states of the dynamical system as it moves towards regions of instability, especially when conventional electrographic monitoring is proven inefficient. Unorthodox cases, with little or no scalp electrographic correlate, in which ictogenic circuitry and/or seizure spread is temporally restricted to neurovegetative, cognitive, and motivational areas are shown as possible explanations for sudden death in epilepsy (SUDEP) and other psychiatric comorbidities. In short, this review presents a paradigm shift in the way that we address the disease and is aimed to encourage debate rather than narrow the rationale epilepsy is currently engaged in.

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1. Introduction

It is not certain where or when epilepsies have become so intrinsically associated with brain excitability. Taken from documented evidence of very early civilizations, it is clear that since the beginning, it was believed that those unfortunate souls carrying the disease would be subject to episodes, in which, some very powerful "unnatural" force would seize control of their bodies [1]. Many should be commended for nowadays modern understanding that epilepsy is, in fact, a disease of the nervous system; nevertheless, much of the early dogmas describing the sudden attack have been reformulated in terms of hyperexcitability and hypersynchronism of neural activity [2]. One such conceptual model proposed by W.G. Lennox even came with a pictorial representation of the excitation/inhibition imbalance in the form of a reservoir or dam of water depicting fundamental and contributing causes that, if surpassing a certain threshold of control, could rupture and produce seizures [3]. In addition, evidence from the success of early treatment with sedatives and or depressants, as potassium bromide and phenobarbital, along with later antiepileptic drugs (AEDs) aimed to decrease neuronal activity (e.g., especially targeting voltage-gated sodium channels) [4] helped to consolidate the reasoning framework for epileptology based on excitability–inhibition imbalance causing hypersynchronous activity that, in turn, would lead to seizures. Several other reports have defended the strong "entanglement" that exists between excitability and synchronism using distinct experimental approaches [5–9]. However, as promising as the whole endeavor looked in the early twentieth century, the "boom" of new AEDs after 1980, i.e., after sodium valproate, failed to significantly

* Corresponding author at: Núcleo de Neurociências, Departamento de Fisiologia e Biofísica, Instituto de Ciências Biológicas, Universidade Federal de Minas Gerais, Av. Antônio Carlos, 6627, CEP 31270-901 Belo Horizonte, MG, Brazil.
E-mail address: mfdm@icb.ufmg.br (M.F.D. Moraes).

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contribute to further controlling seizures in patients with epilepsy that were not yet treatable by previous medication [10] — although considerably impacting on known side effects. Our ever-increasing knowledge of the brain and its functions have driven epileptologists to attempt to understand and explain seizures in terms of neurons, neural circuits, and modulating factors of neural network activity [11] that would describe, in neurobiological terms, how a seizure starts, spreads, maintains sustained activity, compromises normal brain function, and finally, subsides [12]. Such integrative and evidence-based approaches have allowed epileptologists to view excitability and synchronism, although correlated, as two distinct phenomena — owing much to neuroscience techniques that have improved both temporal and spatial resolution measurements of network activation. Accordingly, the very practical and operational definition of a seizure may sometimes encompass some natural phenomena, without any obvious clinical manifestation, and/or, in other cases, some very typical clinically distinguishable events that may not share common mechanisms with the epileptic syndrome. The following sections will challenge the aforementioned orthodox view of epilepsy (i.e., grounded on strictly cellular and/or molecular causes) and shift towards a more integrative perspective, based on deviations from normal brain physiology, in which temporal/dynamical aspects of the complex interactions between brain regions play a more influential role.

1.1. Electrographic signatures, what do they mean

For any specific ion where the chemical and electrical energy gradients are not balanced, permeability will determine the transmembrane flux of charges [13,14]. As a counter example, it is said that GABAergic inhibitory synapses contribute to a lesser extent to extracellularly recorded variations in voltage, because of the fact that near-to-none transmembrane current is generated during chloride changes in permeability because the chemical and electrical energies are in equilibrium for this specific ion [15]. Elaborating on the subject, if present, the effect of a transmembrane ion flux from the extracellular space into the intracellular region, or vice versa, will generate, respectively, a sink or source that will consequently produce an electric field that, in turn, will propagate at the speed of light throughout the brain's conducting media. This is fundamentally the reason why scalp electroencephalogram (EEG) is attributed primarily to excitatory synapses that are spatially organized in such a way that neighboring dipoles may add-up enhancing the produced electric field. Such a neuronal activity-dependent generated electric field may be recorded, almost instantaneously, from electrodes positioned in the extracellular space, making it a very interesting measurement to correlate with behavior, because of its intrinsic high temporal resolution [16]. All things remaining equal, the closer the recording electrode is from a sink or source, the larger will be the voltage change per spatial gradient. This property, along with phase inversions recorded as neighboring channels swipe through a dipole generator, is among the key elements used in neurology to identify the origin of abnormal interictal or ictal activity [17]. Nevertheless, one could have very similar extracellular voltage recordings from a very different combination of sink/source dipoles (the inverse problem of EEG); thus, configuring one of the major setbacks of the electrophysiological recordings — its poor spatial resolution [18]. This undesired characteristic may be partially addressed by recording, when possible, from several different targets at once.

It is important to highlight that the sinks/sources are dynamical in both time and space as a specific neural circuit is sequentially recruited during the flow of information throughout the brain [19]. The electrographic recording, even when made from a distance from possible generators, may have embedded in its waveform/pattern and repetition important clinical cues regarding the improper activation of circuitry associated with diseases [17]. The bottleneck of sink/source propagation delays throughout a neuronal circuit would definitely be at the synapse level; these are the lessons that we can learn from evoked potential recordings (EPRs). In a nutshell, EPRs are time-windowed electrophysiological recordings triggered to a distinct input stimulus. Any voltage changes in the EPR window that are not specifically generated by the input stimulus will have a stochastic distribution at any specific time with a mean equal to zero [20,21]. Thus, EPRs triggered by acoustic stimulation have very similar extracellular recorded potential waveforms, with peaks at very similar latencies, even when recorded from different species with significantly different circuit sizes [22,23] — but with the same overall primary auditory pathway structure and number of synapses [24]. Thus, the EPR electrographic signature seen from the scalp, or any distant vantage point, is actually the algebraic summation of each individual dipole generator while accounting for the exponential decay of electric potentials throughout the extracellular conducting media [16]. Fig. 1 shows a pictorial example of how neural circuit motifs, organized in a very particular sequence, could render a distinct electrographic signature composed of the summated contribution of each individual pattern. As an example, in a work using auditory-evoked potentials (AEP), Moraes et al. [25] recorded from 360 different sites encompassing a $5 \times 6 \times 12$ matrix within the primary auditory midbrain pathway. In this work, the authors showed that the specific morphology of the AEP seen from the scalp could be interpreted as a composed weighted average from each individual in-depth recording. Furthermore, in a follow-up article [26], the authors used a vector-EEG-based technique to make a 3-dimensional current source density analysis and determine the temporal and spatial evolution for dipole generators forming the brainstem auditory-evoked potential waveform. The claim that local field potential (LFP) signatures are actually the summation of multiple circuit motifs activated at once can also be made for "spontaneously" recruited circuits that have very characteristic electrographic waveform morphology, such as fast-wave ripples [27,28] (Fig. 2). The repetition of a specific activation sequence on the phase-space representation of any dynamical system may be interpreted as trajectories (oscillations) centered on an attractor point [29]. Disturbances on the neural network activation pattern (e.g., excitability increasing, external stimuli, different inputs) may alter the trajectory and lead the system's state to orbit another attractor. The interpretation of the repetitive activity as a system trajectory determined by stability–instability transitions is quite interesting for the study of the ictogenic progress on the epileptic brain [30].

Considering the above-referenced discussion on electrographic signatures, the fact that, during most epileptic seizures, there seems to be a very distinct pattern of discharge repeating itself over time is quite suggestive that the same circuit sequence is being recruited over and over again. Whether there is a focal oscillating generator that triggers downstream circuitry [31], a reverberant circuit providing positive feedback [32] or both is still a matter under debate and may differ for specific manifestations within the epilepsy spectrum syndrome. De Guzman et al. [33] showed that hippocampal slices subjected to chemically induced epileptiform activity significantly change their discharge pattern if lesions disrupt different stages of circuitry connectivity; nevertheless, each isolated circuit would still oscillate at a completely independent frequency. Imamura et al. [34] had previously shown that the same pattern change happens if hippocampal transections are made in an in-vivo seizure model of kainic acid injections in the amygdaloid complex. In fact, by disrupting the circuit, Imamura and colleagues were able to significantly attenuate the seizures.

Using a strain of animals inbred to be seizure-prone (i.e., genetically epilepsy prone rats [GEPRs]), Moraes and colleagues showed that not only the repetitive electrographic signature during GEPR9 sound-induced seizure slows down with each recurrent activation of the circuit [35], but that the signature pattern is composed by the recruitment of cortical–thalamic–brainstem circuit firing in sequence [36]. Fig. 3 shows the rationale of the vector-EEG analysis used in the work and how it allows for the decomposition of different parts of the epileptiform electrographic signature in terms of possible generators. A sectioning lesion experiment was used to verify if the interruption of the midbrain to the forebrain connections would affect specifically the part of the

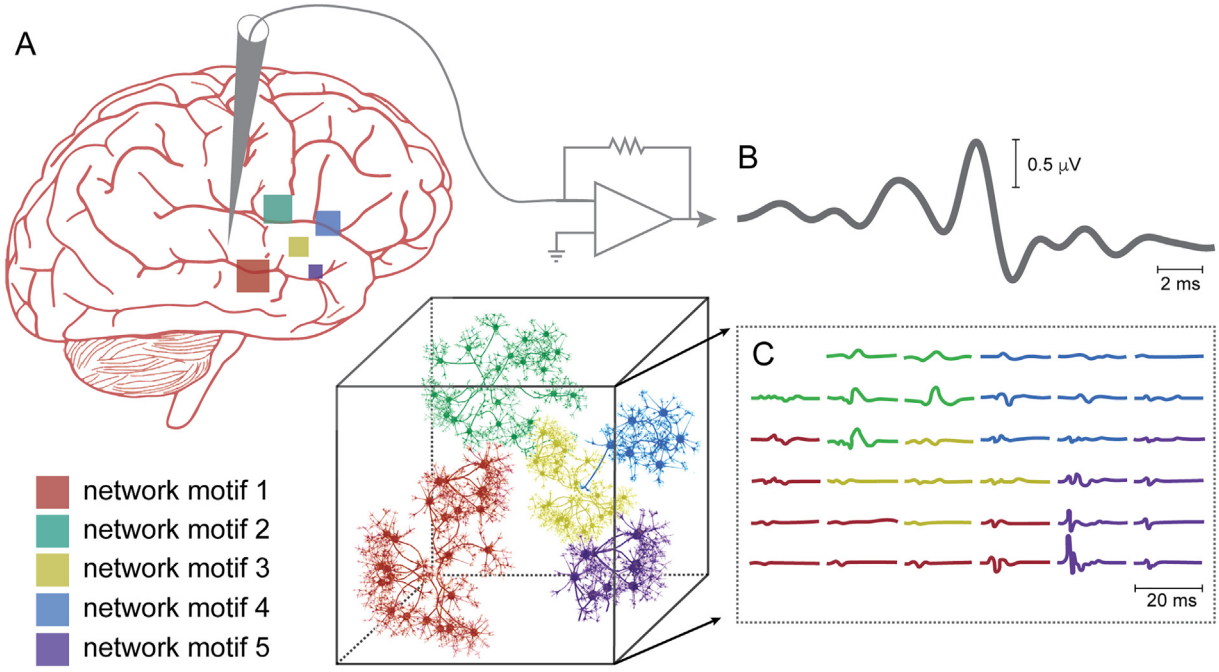

Fig. 1. Electrographic signatures and contributors — Pictorial representation of different networks (cube) and the respective electrographic signatures (C) recorded from a dorsoventral and anteroposterior manner (bottom-right board). The summation of each pattern, if seen from a distance, composes the distinct electrographic signature (gray signal — B) recorded from a specific brain region (A).

electrographic signature associated with the correspondent neuronal generators excised from the circuit [36]. The expected change in discharge pattern waveform morphology occurred as predicted, although the seizure motor manifestation did not change significantly. The data suggest that not all circuitry involved during a seizure episode is necessary to elicit the motor convulsive behavior but could be involved in compromising other brain functions. Thus, the classical repetitive epileptiform activity pattern recorded from EEG or LFPs leads may be the result of activating the same circuits in sequence, one after the next [37]. In any case, the disruption of abnormal brain hyperconnectivity would ideally be necessary only when the neural network is spinning out of control or engaging in a clear pathway to instability.

1.2. The importance of temporal dynamics in ictogenic networks: "knowing when is as important as knowing where"

Aside from the ever-present comorbidities that may have devastating consequences for the patient, the epileptic syndrome is mostly characterized by intermittent compromises of brain function, i.e., the sudden attacks or seizures generally unpredictable in time. Thus, the epileptic condition may be viewed as a dynamical system (DynSys) with bifurcations or transitions that may drive the system towards instability zones that trigger seizures [30,37,38]. However, during the intervals in-between seizures, i.e., interictal periods, even if quasiseizure episodes start to erupt, the feedback mechanisms in play are able to drive system back to stability without triggering a full-scale seizure [39]. The interictal period may have useful cues that could aid not only on the diagnosis and therapeutic strategies but also help to predict if the DynSys is progressing to a point of no return that will inevitably lead to seizures, and thus, allow for seizure prediction. In one such example, the interictal period has very characteristic electrographic patterns or waveform signatures, named interictal epileptiform discharges (IEDs), that are typically found in epileptic tissue but not commonly observed in healthy subjects [40,41]. The exact significance of IEDs and what exactly do they represent in terms of the underlying physiopathology of epilepsy is still a matter under great debate; nevertheless, IEDs have been widely used in clinical neurology as a biomarker for epilepsy [42]. The controversy ranges from the IED representing a small scale, very short, self-contained seizure (in which case IED would be a misnomer [43,44]) to the actual recruitment and spreading of an ictal network by an inhibitory feedback circuit that eventually collapses [45]. In addition, the IEDs could represent either an epiphenomena or a circuit attempting to inhibit neuronal hyperexcitability and contain the spread of abnormal epileptiform activity [46], resembling an endogenous anticonvulsive circuit. Other oscillatory patterns that have a more distinct spectral signature than a properly well-defined waveform shape (e.g., low-voltage fast oscillations [47,48], direct current shifts [49], high-frequency oscillations [HFOs] [50]) also have been suggested as biomarkers for seizure initiation or foci. In any case, altogether, these electrographic biomarkers may reflect state variables that express the transition of the brain from normal behavior to an unstable condition. The computational representation of the brain as a DynSys, with pathways connecting different brain states, could be viewed, in neurobiological terms, as sequentially activated neural networks having each a very characteristic electrographic signature [38]. Thus, as increasingly more neural substrates are functionally interconnected in the same epileptogenic activity pattern, the "seizing" circuits spread to a point of no return and self-sustained activation. In such a scenario, the changes in waveform discharge patterns would reflect the gradual and sequential abnormal coupling between circuit motifs that get hijacked by the ictogenic process [51]. Thus, by studying the trajectories of the DynSys, either under normal or controlled external stimulation, it might be possible not only to have a better diagnosis of epilepsy but also to predict ictogenic onset, a holy grail in epilepsy research.

1.3. Interfering with reverberant circuits

A change in paradigm that such a system's view regarding epilepsy would bring to the table is the possibility to interfere with the temporal dynamics of seizure propagation, transient changes in network connectivity, and consequently, restrain seizure spread instead of ubiquitously targeting excitability at a neuronal or synaptic level (e.g., treatment

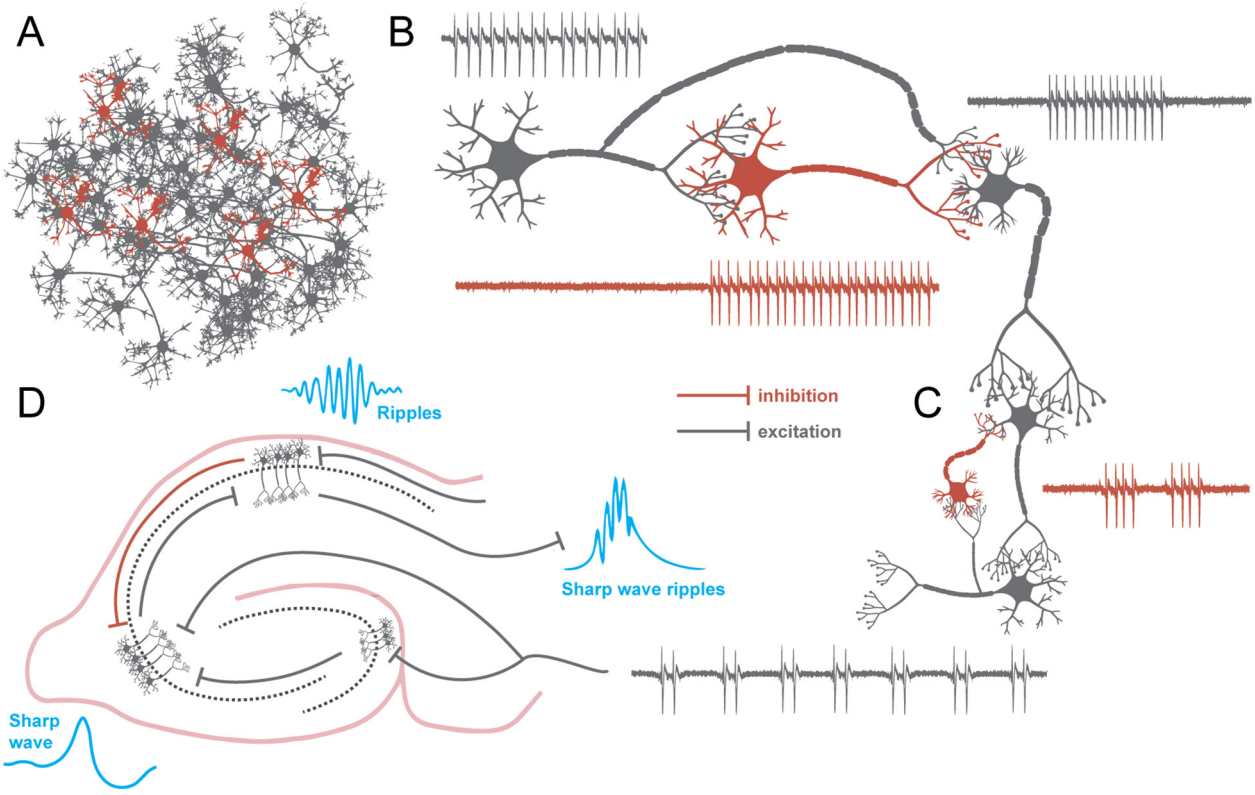

Fig. 2. Example of a neural circuit composed by a feedforward-inhibition (B) and feedback-inhibition (C) motifs (extract from a heterogeneous network — A) and the respective firing pattern of the excitatory (gray) and inhibitory (red) neurons. The association of the circuit output and a complex neural network (hippocampus) may result in the characteristic electrographic waveform morphologies along the hippocampal monosynaptic pathway: sharp waves (CA3), ripples (CA1) and sharp-wave ripples.

with pharmacodepressant drugs). Thus, by limiting the time window of therapeutic interference only to "undesirable" state transitions that will predictively lead to instability, the expected side effects of treatment could be reduced and its effect targeted only at circuits involved in seizure initiation and/or propagation. This lead to the pursuit for fine temporally tuned electrical stimulation carefully designed to modulate synchronization levels as an alternative to treat disorders — epilepsy included — which has been going on for some years now. Such an approach relies on the understanding that baseline synchronism is a mechanism of homeostasis [52], while aberrant synchronism may lead to disease [53]. Moreover, it is akin to the modern view of neurostimulation science and technology that states methods must be properly engineered based on the neurobiological underpinnings of the targeted disorder, instead of only empirically tested [54]. In fact, the coordination of a comprehensive mapping of the electrical wiring of the nervous system, its functions, and rhythms, and a description of disorder-related electrical faults with the corresponding corrective electrical intervention may have inaugurated a new era of disorder treatment termed electroceuticals [55].

In line with this, studies using temporally coded deep-brain electrotherapy designed to desynchronize circuit transient connectivity have been tested both in mathematical seizure models and animal models. One of the first studies on the subject may be the in-silico work of Tass, in which the author designed a stimulation protocol consisting of repetitive double pulses designed to desynchronize clusters of globally coupled phase oscillators. While the first and stronger pulse restarts the cluster, the second one desynchronizes it, once it is aimed for the vulnerable phase of the oscillation [56]. This approach is suggested to be effective in desynchronizing pathological networks in motor disorders such as the Parkinson's disease, but also in epilepsy. In order to overcome the necessity of long calibration periods for the fine-tuning of the delay between pulses, the author has later proposed closing the loop with the method of coordinated reset of neural subpopulations. In this approach, also investigated in silico, the second pulse is substituted by a high-frequency train of pulses delivered in a demand-controlled manner: i.e., when aberrant levels of synchronization, as assessed for instance by local field potential recordings, is detected [57]. After several improvements and studies, authors more recently proposed the multisite delayed feedback method, in which a pulsatile high-frequency stimulation is delivered to different points of an aberrantly synchronized network with pulse amplitudes controlled by linear or nonlinear transformations of recorded neural activity [58]. The authors stated that this may represent a novel closed-loop/demand-controlled and adaptive deep-brain stimulation (DBS) approach to suppress synchronization. Other groups are also pursuing similar approaches of electrical stimulation dependent on neuronal-level activity for the treatment of myriad neurological disorders, including function recovery after brain injury, neurorehabilitation in general [59], and even epilepsy.

Another form of temporally coded stimulation is to temper with the temporal structure of the stimulus itself, instead of only coupling neural activity to the regular firing of pulses in fixed frequency. In fact, the seminal work of Mainen and Sejnowski has shown that neuronal firing activity follows with greater fidelity current amplitudes varying in time according to a Gaussian noise distribution when compared to constant amplitude [60]. Follow-up in-vitro work demonstrated that single neurons [61] and even small networks [62]of cells respond with greater fidelity when stimulation is temporally coded with a power–law distribution of interpulse intervals (for more detail on this, see Cota et al., 2019, in this issue [63]). In line with this, Cota and colleagues devised a nonstandard form of low-frequency electrical stimulation specifically tailored to disturb aberrant synchronization and, thus, suppress epileptic seizures by applying pulses with pseudorandomized interpulse intervals to the basolateral amygdala of rats [64]. The new method termed nonperiodic stimulation (NPS) was shown to have robust

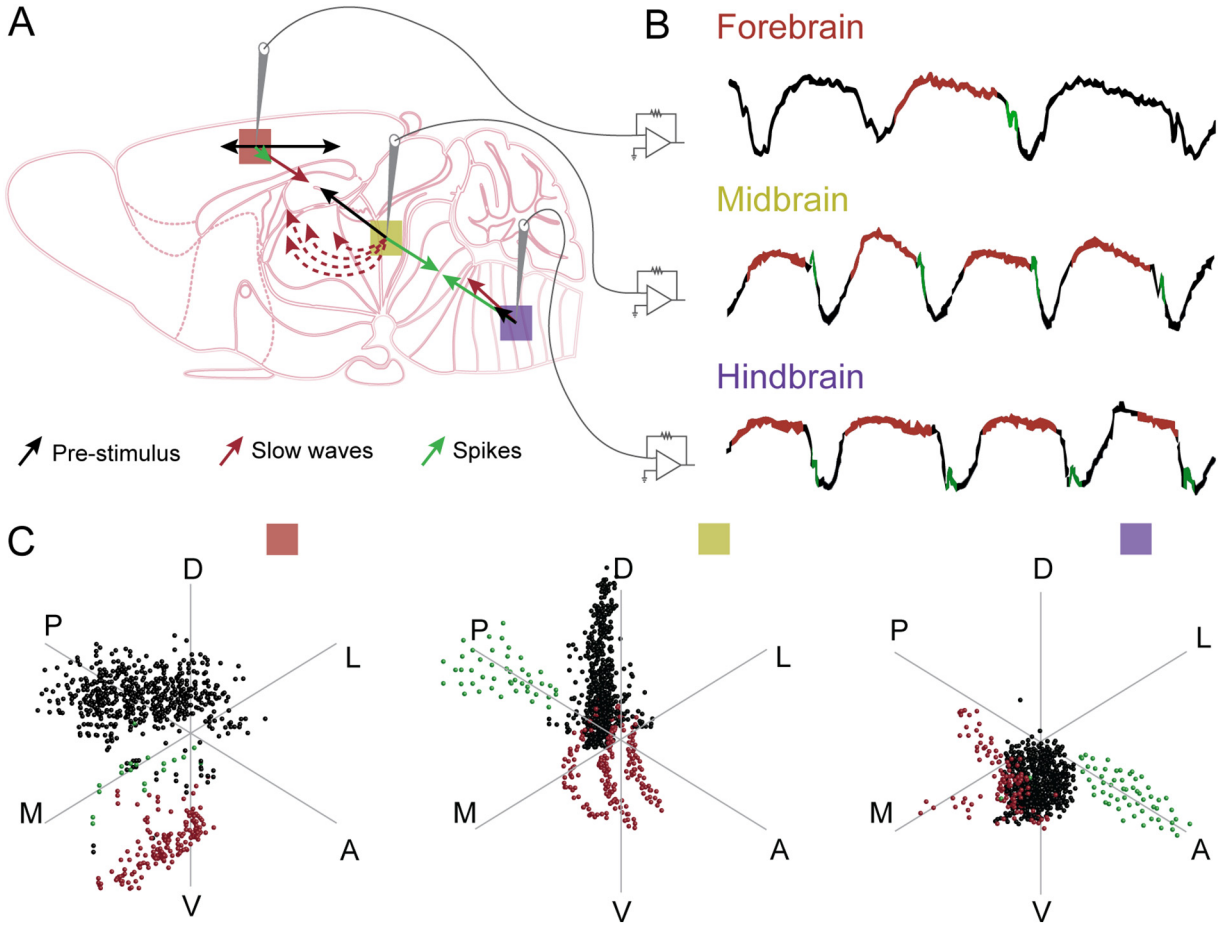

Fig. 3. The rationale of the vector-EEG — Representation of the spike–wave oscillatory pattern (B) recorded from three different positions (A): forebrain (red), midbrain (yellow), and hindbrain (purple). The decomposition of the current sources is exhibited as dots at panel C. Each dot represents the tip of a vector, registering the direction of voltage growth in three-dimensional space axes. The resultant vector (arrows at A) indicates the origin that composes the different parts of the electrographic signature.

anticonvulsant effects against acute seizures induced by controlled infusion of pentylenetetrazole, while other variations in the temporal structure had none whatsoever. The effect has been achieved with an average of only four pulses per second, which is highly desirable given the benefits of increased safety and greater battery longevity of a possible implantable device running such stimulation pattern [65]. Curiously, only the randomization algorithm (two were tried) resulting in interpulse intervals following a power–law distribution was effective in suppressing seizures; NPS has been shown to be also effective in the pilocarpine model of temporal lobe epilepsy [66] and to have enhanced efficacy when applied bilaterally and asynchronously [67]. Investigation on the underlying mechanism of NPS has shown that the amygdala plays an important role in the therapeutic effect [68], which may be attained by direct [69] or indirect (particularly via nucleus accumbens) [63] desynchronization of neural networks enrolled in epileptic phenomena.

Other groups have also applied temporally irregular stimulation to suppress epileptic phenomena or to modulate neural excitation. Santos-Valencia and colleagues [70] successfully delayed electrically induced epileptogenesis in rats using a neurostimulation approach very similar to Cota et al. [64]. On the other hand, using hippocampal stimulation with Poisson-distributed interpulse intervals, Wyckhuys, Buffel, and colleagues were able to reduce spontaneous seizures in the kainate model [70,71] and also to reduce neural excitability in the motor cortex [72], but such effects were attained only with high-frequency stimulation in average. Moreover, Nelson and colleagues investigated whether aperiodicity (Poisson-distributed interpulse intervals) and asynchronicity (no temporal relation between multiple channels of stimulation) play important roles in the suppression of focal seizures model induced by cortical stimulation. They have found out that asynchronous stimuli yielded better results [73]. It is important to highlight that temporally coded activation of neuronal substrates may play an important role in physiological processes as well. If slow-wave rhythms are viewed as propagating up–down states [74,75] throughout the brain, then activation relayed at specific phases of the slow-wave cycle would preferably recruit neural substrates currently in their up-state in the target region. Such an idea has been proposed as a key element in brain architecture [76] in order to provide communication between several small-world networks without overwhelming the parenchyma with white matter, consequently providing a temporal multiplexing framework for information transfer. There are several researchers that published data showing a clear association between a specific task or function to a phase–amplitude correlogram, phase coherence or other temporal correlation mechanisms between brain areas [19,77]. In fact, some psychiatric disorders such as schizophrenia have been shown to compromise the performance and neuronal synchrony during the Mooney face recognition test; a neurological condition comorbid to epilepsy [53]. In order to definitely address the issue if temporal coding could, in fact, be a determining factor in pathway activation emanating from a specific structure, Mourao et al. designed distinct temporal stimulation patterns applied to the amygdaloid complex that differed only in regard to the temporal organization of stimuli — maintaining overall frequency of stimulation, pulse width, intensity, and targeted area [78]. In this work, the authors applied all stimulation patterns, the same number of times, to all animals from several distinct groups; however, choosing only one pattern per group to pair with a

foot shock. Interestingly, only the paired pattern of stimulation was able to elicit the activation of hypothalamic circuitry and freezing behavior. It is also worth mentioning that the temporally structured stimuli were designed to fit within one theta oscillation cycle, having the same number of stimuli falling at different phases of a theta wavelength. These results further corroborate, even during normal physiological processes, that disrupting proper temporal constraints between neuronal substrates can effectively compromise the sequence of activation of a specific circuit pathway.

1.4. Probing networks for abnormal connectivity and facilitated states

The use of passive signal processing analysis of electrographic signals, although more easily applicable, has been suggested to be a less effective approach than active probing of neural circuitry. Clarifying, active probing refers to the triggered provoked and intentional perturbation of neural networks in order to record how they behave and respond to stimuli [79]. Although the above section on passively observing state transitions during interictal brain operation does shed insight on techniques that may be used for seizure diagnosis and prediction, state transitions forcibly induced by external stimulation may allow a better evaluation of networks' abnormal coupling or facilitated self-sustained activity. Studies have successfully shown that the active probing approach improved diagnosis [80], surgical prognosis [81], and seizure prediction [82] when compared to only applying signal processing tools to continuous recordings. Nevertheless, one must be sure that the probing stimuli are safe and relatively innocuous in terms of triggering itself a brain state transition towards instability [83]; otherwise, it could be causing seizures instead of predicting them.

Challenging the usefulness of network probing, one interesting argument is regarding that its efficacy would greatly depend on previous knowledge of what sites should be targeted by stimulation and where to record from. Thus, the whole exercise would resemble a tautological argument in which you need to know where to put the electrodes in order to properly predict where the electrodes should go. Here, we propose two major approaches that justify the use of active probing. First, the choice of stimulating areas should aim to target nuclei with divergent circuits, dense nuclei that project to multiple locations or known pathways that interconnect several brain regions through multiple synaptic relays. In particular, potential candidates for targets should aim to excite pathways that involve ictogenic areas. Also, if multiple electrodes are positioned throughout several depth rods, a trial and error sequence of stimulation paired electrodes can be used to evaluate brain areas with abnormal responses. In a seminal work by Valentin et al., single-pulse electrical stimulation (SPES) was used to determine the prognosis of epilepsy surgery outcome and the identification of epileptogenic zones (EZs) [81]. The same group used SPES to identify epileptogenic tissue in several different brain areas, as a guide to electrode implantation during surgery and also as an inductor of interictal-like activity. The use of electrical stimulation probing in animal models of ictogenesis showed gradual and consistent changes in the evoked responses as it approached seizure onset, thus making it a very interesting prospect for seizure prediction [51]. Another approach uses a modulation frequency to envelop the probing stimulation making it possible to extract from the recordings a specific spectral signature marker for neural substrates responding to stimuli [84]. Pinto et al. used such an approach to show that abnormal circuit connectivity and enhanced network response to the steady-state response (SSR) stimulation was a trait of a strain of animals genetically selected for seizures [85]. Furthermore, the authors show that the dynamics of the SSR alter before seizure onset and undergo a predetermined sequence of changes from seizure onset to the end of the postictal period. Utterly, these strategies are based on the assumption that the circuit encompassed within the probing stimuli input and the recording electrode output will deliver abnormal responses when such circuitry is involved in either the epileptogenic (i.e., structurally modified) or ictogenic (i.e., transiently compromised) processes.

Secondly, It is possible to use the intrinsic plastic properties of the brain to enhance the connectivity from an initially disassociated stimulation targeted area and the ictogenic circuit being probed. Medeiros et al. showed that by pairing amygdala stimulation to a seizure event, the efficacy of the probing stimulation was significantly enhanced in a subsequent induced ictal episode [86]. The idea of having a programmable surrogate marker by pairing an ineffective probing signal to a seizure episode may very well be a solution to cases in which the epileptic foci or underlying pathway of seizure propagation is undetermined or unknown. There is other evidence from literature suggesting that the epileptogenic circuit may not be that different from a poorly formed, generalized memory engram. Bower et al. showed that neuronal assemblies recruited during an epileptic seizure may undergo the same consolidation process during sleep known to occur for any memory trait [87]. In fact, the difference from the physiological proposal of a systems consolidation of memory [88,89] and the pathology in question would lie mostly on the size and indiscriminate recruitment of neighboring engrams characteristic of the epileptic condition.

1.5. When ictal-like neural activity spreads to nonmotor areas

The idea that an electrographic epileptiform signature, or an abnormal response to a probing stimulus, must have its typical clinical manifestation counterpart in order to be called an epileptic event may be a reductionist interpretation of facts. The narrow definition of epilepsy may lead to the exclusion of pathologies that would definitely fall within the same physiopathological mechanisms to those from the epileptic syndrome. Conversely, if the definition of epilepsy is excessively broadened, there may be typical electrographic epileptiform signature-like events in situations where there is no abnormal behavior detected. As an example from the later, spike–wave discharges (SWD) spindles have been suggested to be normal brain rhythms in rodents, being found even in wild-caught rats [90], although very little is known about its physiological significance. In such a case, SWDs are always accompanied by behavioral arrest, and the brain rhythm can be easily interrupted by presenting an adequate external sensory stimulus to the animal, which reinforces the argument of a nonepileptic event. Nevertheless, it could be argued that in epilepsy the circuit generating the SWDs could be hijacked by the epileptic event rendering the pathological brain state unable to stop the rhythm's self-sustained response even when subject to external stimulation [91–93], further elaborating on the conundrum of devising a proper neurobiological definition for an epileptic event, suppose no motor areas are initially involved in the ictogenic process, but the seizure pathway hijacks neuroendocrine regulation or neurovegetative control areas leading to catastrophic consequences and sudden death in epilepsy (SUDEP). It has been shown that audiogenic seizures induced in Wistar audiogenic rats (WARs), a genetic strain of Wistar rats inbred for seizure susceptibility to high-intensity acoustic stimulation, recruit the Paraventricular Nucleus (PVN) and Supraoptic Nucleus (SON) generating a seizure-induced peak of Vasopressin in the bloodstream [94]. Such an activation of neuroendocrine control centers could partially explain cardiovascular alterations in WARs [95,96], as well as other dysfunctions on Motivation–Cognition associated areas [97,98] that could be recruited during, after or even in between the manifestation of motor seizure episodes. In fact, several of the comorbidities associated with epilepsy have been shown, to some extent, to also be present other animal models of epilepsy [99] as well as in WARs [98]. Although still requiring hard evidence for a definitive claim, it has been hypothesized that some of the same mechanisms involved in the hyperexcitability and abnormal synchronization of epilepsy may also be present, possibly in a lesser extent, in the neuropsychiatric comorbidities that accompany the disease — either by resembling subclinical seizures (i.e., that do not spread enough to elicit a full-scale behavioral seizure but elicit psychotic attacks) or by maintaining an elevated connectivity tonus that consequently leads to the compromise of proper brain function [98].

Using a toxic fraction of the *Tityus serrulatus* scorpion (i.e., TytiusToxin — TsTX that targets voltage-gated sodium channels, increasing its conductance to sodium [100]), Guidine et al. were able to generate epileptiform-like discharges, accompanied by its behavioral counterpart, triggered by Intracerebroventricular (i.c.v.) injections of TsTX [101] — also used as an animal model for Epilepsy by other authors [102]. In addition, it was also shown that when such epileptiform activity reached the nucleus of the solitary tract (NTS), animals started to present cardiac arrhythmias that evolved to 3rd degree atrioventricular (AV) blockages and, eventually, to pulmonary edema and death [101]. Although the mechanisms of spread of the epileptic event are most likely associated with the TsTX diffusion on the i.c.v. space, having an epileptic event hijack circuits that control critical aspects of cardiovascular control can lead to death, which sheds light on possible mechanisms for SUDEP. Furthermore, animals were protected from cardiorespiratory failure by cyclodextrin encapsulated carbamazepine (CBZ) injections prior to TsTX-induced seizures even when cortical epileptiform activity was present; other anticonvulsant drugs such as phenobarbital were also shown to block the subsequent pulmonary edema [103,104]. Altogether, these data suggest that if circuits or neural structures are incorporated into the overall ictogenic activity, their functionality may be equally compromised even without any motor manifestation, but severely corrupting neurovegetative control.

1.6. From bench to bedside

Since Sir. Victor Horsley performed the first epilepsy surgery in 1886, the treatment of pharmacoresistant epilepsies relies on identifying an area in which resection, ablation, or disconnection would stop seizure occurrence. At first, the macroscopic lesion and/or cortical stimulated area that reproduces the initial seizure symptoms defined the "discharging lesion," which J.H. Jackson and D. Ferrier believed to be responsible for patient's seizures. Later, after H. Berger [105] reported the first EEG recording, the so-called "discharging zone" evolved to become the EZ. The EZ concept itself evolved throughout the following decades, closely with the invasive recording techniques electrocorticography (ECOG) [106,107], stereo-EEG (SEEG) [108], and subdural grids (SDG) [109,110]. More recently, single-unit action potentials during seizures have shown an even more localized aspect of ictogenesis [111], although present single unit data have not changed the decision-making process in epilepsy treatment.

Epilepsies related to a restricted well-defined epileptic zone/circuit have usually good prognosis, and most of the time can be treated with surgery without invasive recordings or with just trans-operatory invasive registers with good results. Mesial temporal lobe epilepsies or epilepsy secondary to focal cortical dysplasia visible at presurgical noninvasive workup are good examples [112,113].

Patients with extratemporal epilepsy with MRI negative, nonlocalizable scalp EEG, EZ overlap with eloquent area, or multiple lesions that can be related to epileptogenesis are still a challenge. In those patients, even though noninvasive imaging and computational power for signal processing have improved enormously in the last decades, surgical results are still modest [113,114]. The sampling problem is present in all invasive techniques and may be responsible, in part, for struggling in EZ identification. The current paradigm that searches for a single area/circuit sufficient and necessary for seizure generation may not fit all patients, making less probable that a restricted-area intervention could lead to seizure control.

The active probing [66,84,85] associated with image postprocessing [115] can be an interesting approach to reduce sampling problem optimizing invasive electrodes placement. Different methods of invasive active probing like single-pulse electric stimulation [81], but using nonelectric or epileptogenic stimulation, might help to tailor investigation according to physiological circuits involved in a specific patient with epilepsy, like seeing in animal models [85]. The possible strategy to overcome not sampling the EZ would be time coupling the epileptic circuit to a nonepileptic probing circuit similar to the phenomena described by de Castro Medeiros et al. [86]. After coupling, the probing circuit could be used to seizure forecast and or desynchronize the whole epileptic circuit to electric stimulation.

The different modalities of neurostimulation that have shown benefit in epilepsy treatment [116–118] have similar results, despite the fact of being open-loop (vagus nerve stimulation - VNS and DBS) or closed-loop (responsive neurostimulation - RNS and responsive vagus nerve stimulation - rVNS) and direct (RNS) or indirect (VNS and DBS) EZ stimulation. These results raise awareness that the way we deliver and trigger the stimulation should evolve. Once again, active probing and a programmable surrogate marker could help to improve seizure forecast and trigger stimulation, with small interference in physiological function during the interictal period. Using nonperiodic stimulation in order to desynchronize the epileptic circuit, if effective as shown in animal models [64], could increase device battery life and stimulation side effects as previously shown in this manuscript.

The EZ overlapped with an eloquent area and/or composed by multiple noncontiguous brain areas could be accessed focusing on epileptic circuit hubs. The active probing could help to identify these hubs that connects multiple brain regions and can be a target for stimulation, resection, or ablation. The white matter fibers could also be a potential target in cases where cortical and subcortical areas connected are clearly part of the EZ.

2. Conclusion

For years, epilepsy has been seen as a disorder in which hyperexcitability and hypersynchronism are both cause and consequence of the condition, leading to therapeutic strategies that aim to depress neuronal activity and restrict neuronal communication. The temporal aspect of its transient attacks and the sustained activity of seemingly recurrent circuit pathways are incongruous with either the temporal scale of drug-therapy pharmacokinetics or the proposition of a very localized source for all wrong pertaining the disease. New strategies based on a dynamical system's view of epilepsy, encompassing real-time evaluation of shifts in brain states towards instability that are temporally compatible with anticonvulsive feedback strategies must be explored. The view that epilepsy redesigns the brain from a specific dysfunction pertaining to one or more of its isolated elements should be reconsidered or complemented. If a physiological system is driven away from homeostasis, thus, hijacking several functional processes during its evolving stages, the end result could be the plastic rewiring of the brain to facilitate exactly the neuronal networks we name ictogenic. In that case, the understanding of how, why, and when physiological circuitry would cease to perform its proper function and, thus, forced into abnormal behavior is currently helping the development of new prediction and seizure abortion devices.

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Declaration of competing interest

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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