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Review

Toward rational design of electrical stimulation strategies for epilepsy control

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ABSTRACT

Electrical stimulation is emerging as a viable alternative for patients with epilepsy whose seizures are not alleviated by drugs or surgery. Its attractions are temporal and spatial specificity of action, flexibility of waveform parameters and timing, and the perception that its effects are reversible unlike resective surgery. However, despite significant advances in our understanding of mechanisms of neural electrical stimulation, clinical electrotherapy for seizures relies heavily on empirical tuning of parameters and protocols. We highlight concurrent treatment goals with potentially conflicting design constraints that must be resolved when formulating rational strategies for epilepsy electrotherapy, namely, seizure reduction versus cognitive impairment, stimulation efficacy versus tissue safety, and mechanistic insight versus clinical pragmatism. First, treatment markers, objectives, and metrics relevant to electrical stimulation for epilepsy are discussed from a clinical perspective. Then the experimental perspective is presented, with the biophysical mechanisms and modalities of open-loop electrical stimulation, and the potential benefits of closed-loop control for epilepsy.

> The created universe carries the yin at its back and the yang in front;
> Through the union of the pervading principles it reaches harmony.
>
> –from the Tao Te Ching by Lao Tzu

1. Introduction

Over the past two decades, an increasing number of clinical studies have looked to electrical stimulation as a viable option for treating medically refractory epilepsy, probably because of: (1) its perceived flexibility, including the ability to customize, reverse, and adapt treatment; (2) the impression that it is less invasive than resective surgery; and (3) the potential for specifically targeting pathological neural function beyond just a functional lesion of an anatomical target. The mechanisms of electrotherapy may be distinct from those of pharmacotherapy and, therefore, of potential benefit for patients with intractable seizures, more so due to the absence of iatrogenic side effects commonly observed with antiepileptic drugs. However, the ability to design *rational* strategies for epilepsy electrotherapy that take advantage of these features requires an appreciation of: (1) the etiology and pathophysiology of epilepsy; (2) the mechanisms by which electrical stimulation interacts with the nervous system and modulates function at the cellular, synaptic, and network levels; and (3) the spectrum of potential hazards associated with electrical stimulation and the limitations of the stimulation hardware. These aspects are intimately related on multiple levels, and the tensions within and across these levels—likened here to "*yin–yang*" interactions [1]—must be considered both in the big picture and in our individual pursuits toward electrotherapy design.

In this article, we do not attempt to provide an introduction to epilepsy control [2–6], or a historical review and critique of various approaches [7]. Instead, we identify central challenges in the rational electrical treatment of epilepsy through different lenses summarized by three questions: (1) What are seizures and what does it mean to control them? (2) What does electrical stimulation do to neural tissue? (3) What are the side effects, instrumentation requirements, and safety limitations? Successful therapy depends on understanding and addressing these questions, and recognizing that they jointly determine treatment constraints.

The principal considerations in the electrical treatment of epilepsy and their interrelationships may be visualized using a pinwheel structure (Fig. 1) with the desired goal, an optimal strategy for electrical stimulation, at its center informed collectively by three

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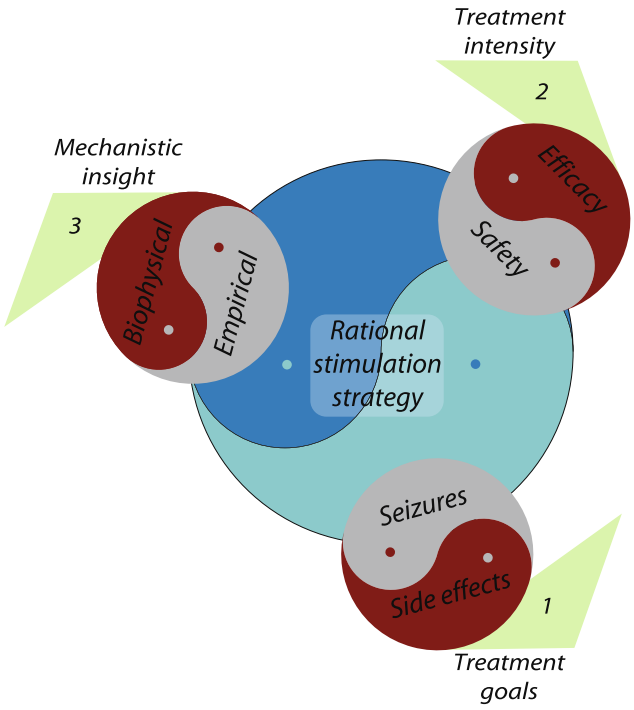

Fig. 1. Pinwheel of rational electrotherapy. Conflicting design factors related to (1) treatment goals, (2) treatment intensity, and (3) mechanistic insight, depicted here as yin–yang interactions, that must be resolved in the formulation of a rational electrical stimulation strategy for the treatment of epilepsy.

conceptual blades. Each blade is double-edged, and symbolizes: (1) alleviation of seizures (or related dynamical markers) by stimulation, but accompanied by potentially adverse effects on cognition and behavior; (2) more effective treatment achieved by increasing stimulation invasiveness and intensity, but with an elevated risk of tissue damage; and (3) the disconnect between clinical trials, in which empirical selection of stimulation parameters is still the norm, and insight into the biophysical effects of stimulation derived from basic research studies, particularly those performed at the cellular and small network levels. The careful resolution of these various conflicts—yin–yang design—is essential for turning the wheel of therapy firmly toward the rational treatment of epilepsy.

In the absence of a comprehensive biophysical understanding of these factors, clinical efforts at electrical epilepsy treatment (reviewed by Sun et al. [8], Krauss and Koubeissi [9], Pollo and Villemure [10], and Benabid [11]) use stimulation technology and protocols that are largely empirically derived, and usually adapted from approaches to treat disparate conditions such as movement disorders. Conversely, in animal and computational studies, the effects of electrical stimulation on seizures have been studied at the cellular and network levels often without appropriate regard for practical clinical factors. This review outlines some considerations required to bridge these endeavors and move the field toward a more integrated design of electrical seizure control systems. Indeed, the need to articulate such information comes in part from our own experience and naiveté in attempting to contribute on the biophysical side, often with blinders to some of the broader issues involved in a whole-system solution.

2. Clinical aspects of epilepsy and objectives for electrotherapy

2.1. Seizures and epilepsy

What are seizures? Epilepsy is characterized by recurrent episodes of paroxysmal neural discharge known as seizures. The seizures themselves are events in which normal behavior may be altered and cognitive control or consciousness *seized* or taken away. Electrical recordings of brain activity—electroencephalograms (EEGs)—often have stereotypical, abnormally large-amplitude rhythmic patterns during seizures. The cause of seizures is commonly attributed to an "imbalance in excitation and inhibition" leading to "hyperexcitable" and "hypersynchronous" neuronal activity (see reviews by Engel [12], Scharfman [13], and Jefferys [14]) though more nuanced alternative hypotheses based on single cell electrophysiological recordings have been proposed [15,16]. It is recognized that human epilepsy reflects a constellation of disorders, with different underlying pathophysiologies and anatomical foci.

Seizures are a symptom of epilepsy, which has many possible etiologies: genetic abnormalities [17], channelopathies [18], hippocampal sclerosis [19], traumatic brain injury [20], and glial dysfunction [21], to name a few. The combination of etiology, medical history, and the part(s) of the brain affected can give rise to different epilepsy syndromes and seizure types. Apart from seizures, important consequences or comorbidities of epilepsy include cognitive impairment, depression, loss of work or driving privileges, and sleep disorders. Notwithstanding these factors, alleviation of seizures is almost always the primary endpoint of treatment (see Section 2.2).

The existence of a *preseizure* state has been postulated. Although the search for this preseizure state—the subject of many clinical and laboratory investigations—is yet to bear edible fruit [22], it brings into focus the first main aspect of the rational electrotherapy design process that must be addressed: Epilepsy is the manifestation of a highly complex dynamical system, and seizures constitute but one of many states that the system occupies. We must ask: With what aspect of the dynamic do we intend to interact? What control laws should be used to achieve what dynamical objectives? And with what aspects do we directly or collaterally interact? These questions are especially relevant to the timing of therapy if, for instance, stimulation does not suppress an ongoing seizure but is effective when applied prior to seizure initiation.

2.2. Prerequisites for rational electrotherapy

Rational electrotherapy involves the control or titration of stimulation dosage based on a meaningful assessment of stimulation outcome—the focus of this section—and an understanding of stimulation tools and mechanisms, which we address in Section 3.

The following considerations apply for rational quantitative assessment and improvement of clinical treatment: (1) identification of a *treatment marker(s)*, that is, the symptom, event, or condition that is the focus of treatment, with associated performance goals in the form of an endpoint and/or cost function, where achieving these endpoints is the *treatment objective*; and (2) formulation of *treatment metrics*, that is, suitable behavioral/physiological measures for use in programming and evaluating treatment that quantify relevant features of the treatment marker(s). These requirements are equally relevant to translational animal studies.

2.2.1. Treatment markers and objectives

Without question, the primary treatment *marker* or event of interest in epilepsy therapy is the seizure. The primary *objective* is the reduction of seizure frequency and severity, particularly *clinical* seizures.

Nevertheless, the question of what aspect of seizure dynamics should be targeted and how to interact with it is critical and nontrivial. For example, what are the consequences of modifying seizure intensity, duration, or spread when complete suppression is not practical? When an epileptiform event has started or is immi-