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Rational design of transcranial alternating current stimulation: Identification, engagement, and validation of network oscillations as treatment targets

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Abstract

Network oscillations in the brain are routinely recorded in the clinic and in the research lab. Here we outline a new paradigm in which network oscillations serve as treatment targets for noninvasive brain stimulation. We show how transcranial alternating current stimulation (tACS) can be used to modulate network oscillations that are impaired in disorders of the central nervous system (CNS). Using rational design, a structured process of target identification, target engagement, and target validation can be deployed to develop effective noninvasive brain stimulation paradigms for the treatment of neurological and psychiatric illnesses. We conclude by outlining how this approach could be applied to two disorders of the CNS, depression and epilepsy, for which there already exist clinical brain stimulation treatment options.

Keywords

Network oscillations, noninvasive brain stimulation, tACS, CNS disorders, target identification, target engagement, target validation, treatment

Rhythmic structure is one of the main features of neuronal activity.[1,2] Since the discovery of the electroencephalogram (EEG) by Hans Berger early in the 20th century,[3] it has been known that human brain activity measured at the macroscale by scalp electrodes exhibits oscillatory features. We today know that the rhythmic structure emerges through complex interactions of intrinsic, synaptic, and non-synaptic mechanisms, resulting in synchronization, which leads to a superimposition of the weak electric fields generated by individual neuronal elements. The emergent macroscopic electric field thus reflects the coordinated activity of a large number of neurons. Remarkably, the study and interpretation of brain rhythms have taken very different forms, depending on the specific scientific field and clinical discipline. For example, epileptology and sleep medicine have a long history of defining pathological states and conditions through the presence of specific oscillatory features in the EEG. Strikingly, the clinical

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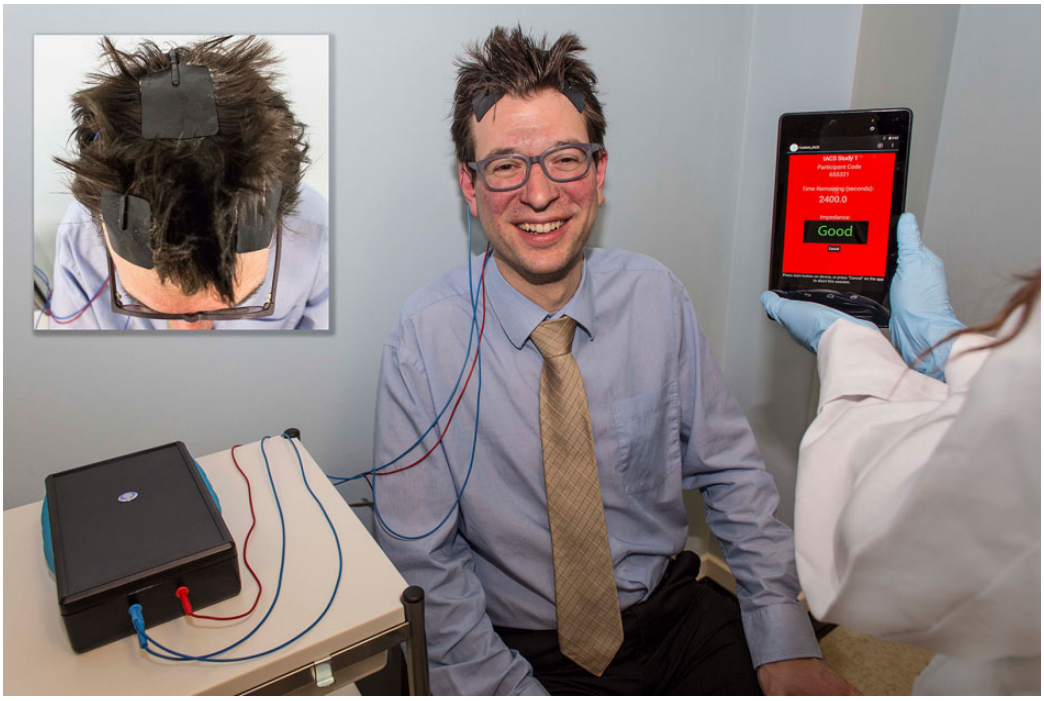

Figure 1. tACS can be applied with portable, battery-powered devices as the one shown here developed by one of the authors (FF). Stimulation current is delivered by electrically conducting silicone–carbon electrodes (inset), which are attached to the scalp with conducting paste typically used for attaching EEG electrodes. The electrodes are relatively large (typically 5 × 5 cm) for broad spatial reach of the resulting electric field. The shown montage has been used in a number of our clinical trials in which we targeted deficits in large-scale brain functional connectivity in the alpha frequency band. tACS: transcranial alternating current stimulation; EEG: electroencephalogram. Photo credit: Morgan Alexander.

conceptualization of pathological changes in brain rhythms still mostly relies on the visual examination of EEG traces. In stark contrast, there are neuroscience research communities that have traditionally discounted the presence of the rhythmic organization measured by EEG (or as a local field potential (LFP) from implanted electrodes in animal models) as an epiphenomenon. The recent advent of transcranial alternating current stimulation (tACS) has revitalized and partially resolved this debate about the causal role of brain rhythms. This novel form of noninvasive brain stimulation applies a weak sine-wave current to the brain via scalp electrodes (Figure 1). With tACS, there is now a safe tool at our disposal for noninvasive, targeted modulation of human brain rhythms. What makes tACS attractive is that the required hardware is lightweight and relatively cheap, thus offering the opportunity of mobile and widespread deployment of this brain stimulation technology. The obvious and exciting application of tACS in human neuroscience is to modulate a specific brain rhythm and determine changes in cognition and behavior that have been associated with this rhythm in previous EEG studies. A quickly growing number of studies have been able to demonstrate such causal links between brain oscillations and specific cognitive functions such as working memory.[4] A comprehensive review would be beyond the scope of this article. Rather, we here focus on outlining a novel approach of leveraging tACS as a neurotherapeutic for disorders of the nervous system. In particular, we are developing a rational design approach for the development of tACS as clinical treatment tool. This approach is enabled by a tight integration of research strategies from biology, engineering, and medicine. The fundamental challenge of tACS (and many other types of brain stimulation) is that there are uncountable parameter combinations that can be used for stimulation paradigms. Any attempt of a detailed parameter exploration is thus bound to fail. Rational design serves as a potential solution since it strives to gain a mechanistic understanding of how tACS works, which will then allow the theory-driven choice of optimal/optimized parameters. In this approach, there are in essence three interlocked steps, which we refer to as *target identification*, *target engagement*, and *target validation*. Briefly, target identification refers to work that aims to delineate how neuronal oscillations mediate cognition and behavior and how these oscillations are impaired in disease states. Necessarily, this approach includes gaining a detailed biophysical understanding of how these oscillations are generated. Target engagement focuses on identifying how stimulation paradigms modulate brain rhythms with the goal of identifying theoretical principles. Target validation refers to the (subsequent) investigation if oscillation dynamics can indeed be restored and—most importantly—if restoring the network

neurophysiology indeed improves symptoms in patient populations. Thus, target validation studies necessarily include clinical outcomes together with neurophysiological measures such as EEG.

Target identification

There is a rich literature of studying network oscillations in systems neuroscience. Most studies have been performed in rats and mice. For example, encoding of space and time in the context of memory has been thoroughly investigated in the rodent hippocampus.[5] Synchronization of several rhythmic activity patterns plays a fundamental role in that circuit. Similarly, thanks to the relative ease of genetic perturbations in mice, there is a number of "animal models" of psychiatric and other central nervous system (CNS) disorders. In that sense, one could conclude that there exists a rich literature that serves the purpose of target identification. Unfortunately, however, it has turned out that reality is more complex than that. One striking example is the alpha oscillation, a ubiquitous thalamocortical rhythm in humans. The alpha oscillation is not present in small rodents, perhaps due to the relative simplicity of the (visual) thalamocortical system. The resulting gap between mice and men represents a significant hurdle in the development of targets for noninvasive brain stimulation in humans. In addition, there is a growing consensus that there is no "depressed mouse" or "mouse with schizophrenia" since these complex psychiatric disorders are in many ways truly human. This becomes very evident when one considers how simple the behavioral assessments of "disease" are in mouse studies. Together, the focus on mouse research over the last decade has created a significant delay in the necessary science for target identification and ultimately successful translation to new treatments with brain stimulation (or other innovative therapeutic strategy that are designed to target network pathology). One strategy forward is the development of animal models that have a broader shared substrate of structural and functional network connectivity with humans. For example, one of the authors (FF) has adapted the application of many of the cutting-edge systems neuroscience techniques such as optogenetic perturbations,[6] functional magnetic resonance imaging (fMRI),[7] and touch screen–based cognitive assays[8] to the ferret (*Mustela putorius furo*). The ferret is a domesticated carnivore with a gyrencephalic brain, with a well-defined prefrontal cortex (resembling the dorsolateral prefrontal cortex in primates[9]) that is missing in mice. Also, the ferret has a quite well developed visual system that includes columnar cortical organization, primate-like pulvinar complex (extrageniculate visual thalamus), and a brain size that easily allows for multisite electrical recordings of brain activity with implanted electrodes. In fact, we have recently demonstrated the clear presence of thalamocortical alpha oscillations that are (like in humans) gated by arousal.[10] These oscillations occurred in the structurally connected system of posterior parietal cortex and pulvinar complex[11] again in similarity to primates. While this is an early step, this example demonstrates that by working with other small mammals, model organisms can be developed that share important features such as the alpha oscillations, which is known to be impaired in range of psychiatric disorders, including depression and schizophrenia.[12,13]

Target engagement

The first and most important question in the context of modulating brain rhythms with tACS is if and how a very weak electric field can modulate cortical rhythmic activity. It has been known for quite a while that electric fields, when properly aligned to the main somatodendritic axis, can depolarize neurons.[14] This depolarization is, conceptually spoken, the consequence of the relative electric isolation of the cytosol (inside of the cell) from the extracellular space (by the cell membrane). When an electric field is applied, it imposes an extracellular gradient of electric potential. In contrast, in the cytosol, charge carriers (i.e. ions) reorganize their position until the electrical field is cancelled out. Since the membrane voltage is measured as the difference between inside and outside of the cell, the net consequence is an electrical polarization of the neuron. The original interest in the effect of weak electric fields was motivated by the question whether endogenous electric fields that emerge from meso- and macroscale neuronal synchronization (measured as LFP or EEG) may influence neuronal activity. This hypothesis was mostly abandoned since the changes in membrane potential by exposure to an electric field are very small. The (erroneous) conclusion is that a perturbation that does not trigger an action potential, that is, a "subthreshold" perturbation, cannot modulate neuronal activity. It is worth dissecting this fallacy. First, the distinction into sub- and suprathreshold perturbations is an artificial one with little benefit to understanding the effect of electromagnetic fields applied to the nervous system. The membrane voltage of neurons is constantly fluctuating as a function of synaptic input and intrinsic ion channel dynamics. Thus, a weak perturbation may have indeed little effect on the output of a neuron (firing of an action potential). However, if the neuron is close to threshold for action potential generation, then the same weak input can easily trigger an action potential. As a direct consequence, the effect of weak electric fields on the nervous system needs to be understood in the context of the endogenous network dynamics/oscillations, and the effect of the stimulation is a function of the synergistic interaction with these dynamics. In other words, the effect of stimulation is state-dependent. In addition, it is worth noting that this mechanism of action must include a focus on network dynamics. In fact, when the appropriate closed-loop technology was developed and applied to directly dissect the proposed feedback interaction between neuronal activity and the thereby generate electric

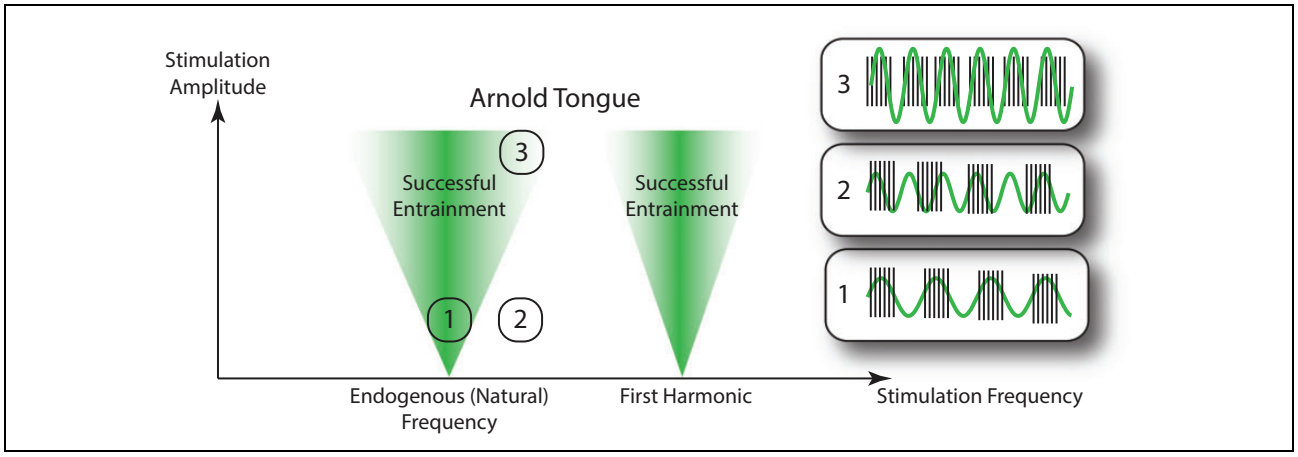

Figure 2. Schematic depiction of the Arnold tongue. Parameter combinations of stimulation amplitude and frequency that cause successful entrainment are marked in green. For small stimulation amplitudes, tuning of the stimulation frequency to the endogenous frequency is crucial (tip of inverted triangles).

field, it was found that weak endogenous electric fields can effectively guide and synchronize neuronal activity.[15]

With this understanding of weak electric fields established, the next question is to identify how stimulation parameters should be chosen to most effectively modulate neuronal activity. Perhaps not surprisingly, the most effective enhancement of oscillations results from stimulation, which is periodic itself (such as the sine-wave used in tACS) and frequency matches to the endogenous network dynamics. Large-scale computer simulations of cortical (and more recently also thalamic networks) propose that a principle from dynamical system theory, the so-called Arnold tongue, applied to the modulation of network oscillations by tACS.[16,17] The Arnold tongue refers to the visual depiction of the combination of stimulation parameters (frequency and amplitude) of a periodic perturbation that successfully entrains an oscillating system (Figure 2). Entrainment is in essence the temporal synchronization of the endogenous dynamics to an applied periodic force. The Arnold tongue resembles an inverted triangle that centers on the endogenous oscillation frequency, for which (in theory) an even infinitely weak perturbation can entrain an oscillator. An important feature of the Arnold tongue is that there are additional "parameter zones" of entrainment at various harmonics of the endogenous oscillation frequency. Confirmation of the Arnold tongue in the living brain is currently pending.

Target validation

The goal is to leverage the insights gained from target engagement studies and to deploy these paradigms in the form of experimental treatment paradigms in clinical trials. It is worth noting that the unique safety profile of tACS has allowed the rapid acceleration of the human research since there are no concerns of unwanted offsite effects in other organ systems. Even in contrast to transcranial magnetic stimulation (TMS), the safety profile of tACS is more favorable since there are no plausible reports of triggering seizures with tACS, which is a rare but important to consider side effect of at least certain TMS paradigms. In addition, the smaller and portable nature of tACS devices make clinical trials with tACS comparatively easy to perform. One of the authors (FF) has recently performed several treatment clinical trials of tACS to establish target engagement and target validation in schizophrenia,[18] depression, and chronic pain. Several more studies are ongoing and presentation of the findings for most of these studies is pending. Given the potential of tACS to serve as platform technology since many disorders of the CNS have been found to be associated with pathological changes in cortical oscillations, there is an urgent need to broaden and deepen the set of clinical trials of tACS to be performed. Importantly, these studies need to be performed as gold standard clinical trials, which unfortunately is not that common in the field. The early transcranial direct current stimulation (tDCS) and tACS literature from the last decade comprises mostly small pilot studies that report large effect sizes. The lack of proper double-blind study design and the inherent publication bias toward positive results that has affected all of biomedical research has created substantial damage to the reputation of the field and needs to be addressed. A clinical trial of tACS (or tDCS) requires a robust double-blind design. From a technical viewpoint, this requires engineering controls that ensure a double-blind study design can be successfully deployed. Small but important glitches can endanger the blind. For example, a stimulation device with a built-in battery and a display of the charge remaining after completion of stimulation seems to be a helpful feature. However, any type of placebo or "sham" stimulation will require significantly less power and thus accidental unblinding by alert study personnel is almost bound to happen. The other important aspect of study design is the requirement to measure target engagement through

electrophysiological or other means. This has been recognized by the National Institute of Mental Health in the United States, which now requires that the primary outcome of clinical studies is a biological variable and not a clinical assessment or symptom score. This shift is justified by the number of large and expensive clinical trials that have failed and provided no biological insights of value due to the lack of such measurements of target engagement. This approach is also referred to as "experimental medicine." For tACS studies, the obvious choice of method to determine target engagement is EEG (or magnetoencephalography, MEG). The temporal resolution of EEG and MEG is needed to establish changes in rhythmic neuronal network activity caused by stimulation. In the subsequent sections, we will outline how the framework of target identification, engagement, and validation could be applied to two disorders of the nervous system, depression and epilepsy.

Depression

The treatment of mood disorders with brain stimulation has a long history. Electroconvulsive therapy (ECT), where electrical stimulation is applied to elicit electrographic seizures, is an effective treatment for depression.[19] However, the procedure is quite involved since it requires general anesthesia and some patients report cognitive side effects. The underlying mechanism of action remains to be fully elucidated. Conceptually, ECT aims to override endogenous network dynamics. Driven by the success of ECT, stimulation paradigms that deliver less energy and are thus (perceived as) more tolerable have been under development. The first major breakthrough in this development was TMS,[20] which now has regulatory clearance in many countries. TMS delivers a strong magnetic field via a stimulation coil. The stimulation amplitude is typically normalized to the amplitude required to elicit a muscle response by stimulation of motor cortex. The standard clinical TMS paradigm consists of 10 Hz stimulation, applied for few tens of stimulation sessions. Given the electromagnetic properties of live tissue, TMS can be spatially targeted since the magnetic field does not spread in tissue. Thus, in combination with MRI and computer vision, "neuronavigation" can be performed to apply the magnetic field to a spatially defined location at the surface of the brain. Thus, in contrast to tACS, where the stimulation current generates a spatially diffuse electric field in the brain, specificity of stimulation in TMS focuses on space and not time. The stimulation location for the treatment of depression is the dorsolateral prefrontal cortex (dl-PFC). This target is based on a large set of imaging findings, which support hypoactivity of left frontal areas as a network marker of depression.[21] Interestingly, the amount of evidence for the successful target engagement through imaging, that is, restoration or enhancement of left frontal activity with fMRI, remains limited.[22] The stimulation waveform used in TMS is partially constrained by the technology of the delivery of the magnetic field and the tolerability of the stimulation due to activation of nerves in the scalp. Importantly, the choice of 10 Hz has thus not been guided by an identified target (temporal dynamics). What is remarkable about TMS is that the 10 Hz stimulation frequency falls within the alpha frequency band (8–12 Hz) and that a short sequence of 10 Hz TMS pulses entrains alpha oscillations, at least in healthy control participants.[23] Together with the (relatively consistent) findings of pathologically altered alpha oscillations in depression, it appears fair to speculate that the potential mechanism of action of TMS is through modulation of alpha oscillations. Yet, there are multiple questions that surround the mechanisms of action of TMS since more recent, larger clinical trials that compared stimulation frequencies (10 Hz versus 1 Hz) and stimulation locations (left versus right dl-PFC) have yet to identify clinically meaningful differences in stimulation outcomes.[24] More recently, attempts to develop stimulation paradigms for depression that use even less energy have been pursued. For example, synchronized TMS (sTMS) is explicitly based on targeting alpha oscillations.[25] In the sTMS device, a set of static magnets are mounted such that they rotate to generate an electromagnetic field in the frequency range of alpha oscillations. The resulting electric field is presumed to be multiple orders of magnitude lower than in TMS. In a certain way, the underlying approach resembles the proposed target engagement principle of tACS, the Arnold tongue.[26] The stimulation (i.e. magnet rotation) frequency is set to the individual alpha frequency peak of every participant, thus (in theory) situating stimulation at the "tip" of the Arnold tongue, where even very weak electric fields are proposed to entrain (neuronal) oscillation. Remarkably, therapeutic success seemed to depend on if the stimulation frequency was correctly chosen. However, this finding is based on an exploratory analysis and the main intent-to-treat outcome was negative. Nevertheless, one important mechanistic question of target engagement is raised by this work. Alpha oscillations in the left (frontal) hemisphere are pathologically elevated in patients with depression,[27,28] albeit it remains unclear how robust this observation is, given the recent publication of several negative findings and meta-analyses.[29] Assuming these elevated alpha oscillations in the left frontal areas are indeed a marker for depression (and thus a reasonable stimulation target), it remains unclear why a periodic perturbation applied in the stimulation frequency would dampen and not enhance the pathological oscillations.[30] One hypothesis is that repeat enhancement of alpha oscillations ultimately leads to a homeostatic reduction of endogenous alpha oscillations. At this point, there are no experimental data that speaks to this hypothesis. Another hypothesis is that through broad spatial targeting, stimulation can "rebalance" or "redistribute" alpha oscillations and thereby reduce the pathologically elevated left frontal alpha oscillations. These proposed models remain generic

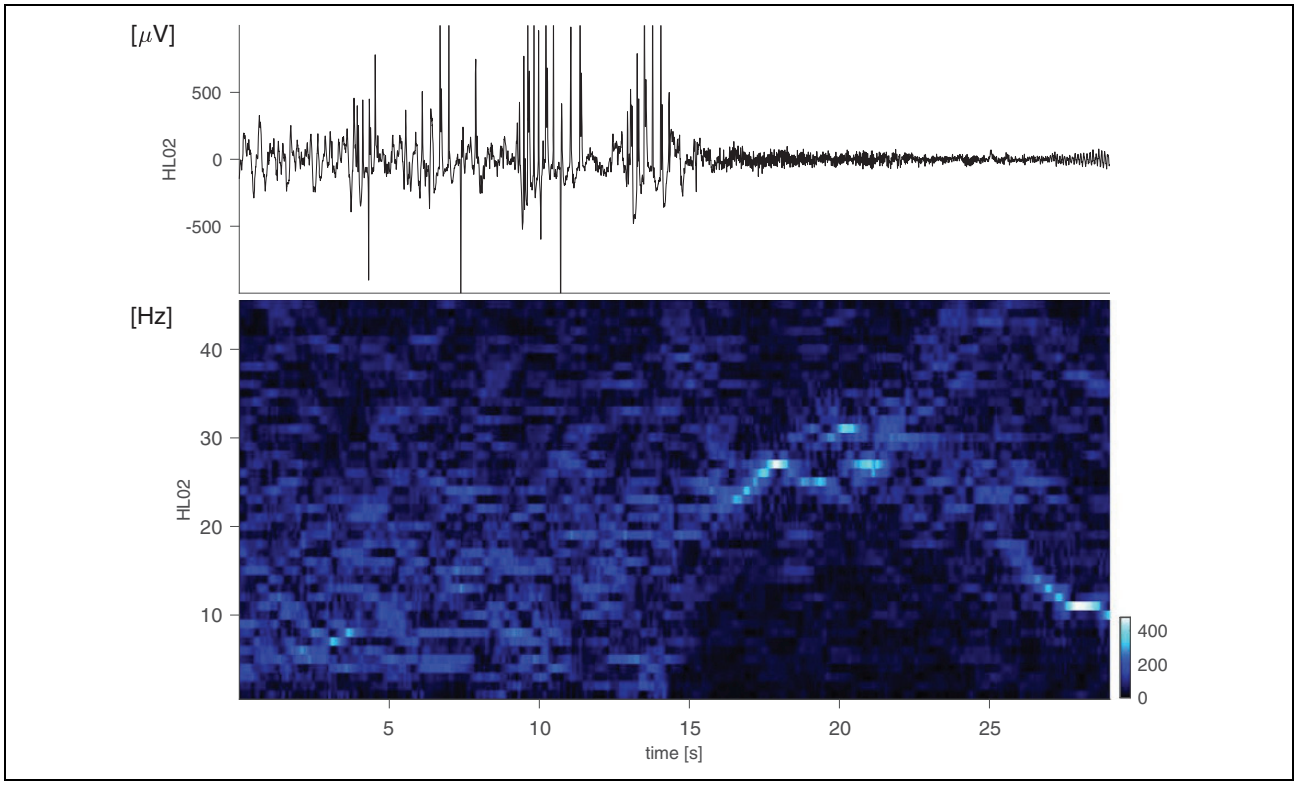

Figure 3. iEEG recorded by a depth electrode placed into the left hippocampal region of a patient with pharmacoresistant epilepsy. At seizure onset, interictal patterns of brain activity—slower signals and spikes—disappear and are replaced by fast oscillations, which are more clearly visualized in the spectrogram.[34] Detecting, engaging, and stabilizing certain interictal patterns might reduce the probability of seizure onset.[35] iEEG: intracranial electroencephalogram.

and more experimental evidence is critically needed. One of the authors (FF) has recently performed the first clinical trial of tACS for the treatment of depression. The study compared 10-Hz tACS (to target alpha oscillations), 40Hz-tACS (control frequency), and sham (placebo) stimulation in a parallel-group design. The publication of the results is pending. In summary, the appreciation of noninvasive brain stimulation from the perspective of the framework of the approach in this article (target identification, target engagement, and target validation) leads to several conclusions. First, there is a trend to move from high-amplitude stimulation approaches that override brain activity to low-amplitude stimulation approaches, which are hypothesized to be more specific since they work by synergistic interaction with endogenous network activity patterns. This effort requires an understanding of the mechanism of action. Second, the therapeutic benefit (and risk/benefit profile) of today's noninvasive brain stimulation modalities for the treatment of depression is likely far from optimal since the stimulation paradigms have yet to be optimized and targeted through rational design.

Epilepsy

Epilepsy is in many ways fundamentally different from depression, yet it is another disease for which there are clinically approved brain stimulation treatments. From the perspective of target identification, epilepsy appears to be the ideal candidate since the disease is defined by aberrant electric network activity patterns, which could thus serve as targets. Yet, the stimulation strategies may need to be different since the obvious goal would be to suppress pathological activity patterns. Thus, the conceptually most straightforward approach is to detect the onset of a seizure and then apply stimulation to disrupt the development of pathological network activity. Intuitively, to "override" large-scale pathological activity, high stimulation amplitudes are required, which may need to be delivered intracranially. Refinement of target engagement strategies such as timing of stimulation informed by dynamical models of seizures could be used to exploit "vulnerabilities/instabilities" of seizure activity patterns. At the level of target validation, similar problems to brain stimulation in depression emerge. The heterogeneity of disease manifestations and the state-dependence of pathological network dynamics make the demonstration of clinical efficacy challenging.

Our framework of target identification, engagement, and validation could also be used for a paradigm-shifting approach to brain stimulation in epilepsy, which focuses on stabilizing and enhancing activity patterns that "protect" the brain from developing seizures. In this approach,

activity patterns which prevent individual subnetworks to "break free" and develop pathological activity[31] would represent the stimulation target. Perhaps counterintuitively and in contradiction to the textbook model of epileptic seizures, low-frequency, synchronized activity patterns may serve as a mechanism to both prevent the development of seizures and also play a crucial role in terminating seizures (Figure 3).[32,33] While more experimental evidence for this refined model is urgently needed, this model would support the use of low-amplitude noninvasive paradigms such as tACS to enhance and stabilize physiological synchronization of networks to prevent the occurrence of seizures. Thus, target identification would focus on delineating the oscillatory modes of "seizure protection." Target engagement would require an understanding if networks in the brain of patients with epilepsy respond equally favorable to the application of tACS and if indeed the same mechanisms such as the Arnold tongue may apply. Finally, target validation studies would have similar structures as for any other brain stimulation study in epilepsy in terms of reducing seizure rate.

Outlook

The integrated approach for the development of novel therapeutic neurotechnology proposed here combines identification, engagement, and validation of network oscillations as targets for tACS. This approach is motivated by the unique synergisms of a multidisciplinary approach that spans from computational neuroscience to clinical trials. As simple as the underlying idea of treating pathologies of endogenous electric fields with exogenous electric fields is, the promise of a safe and effective treatment platform for disorders of the brain propels the approach outlined here is unique and deserves our full attention.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: FF is the lead inventor of brain stimulation technology for which UNC—Chapel Hill has filed several patents. FF is the chief scientific officer and majority owner of Pulvinar Neuro LLC. FF receives author royalties from Elsevier. KS is a consultant for Pulvinar Neuro LLC and for the Wyss Center for Bio and Neuro Engineering in Geneva.

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