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Closed-Loop Transcranial Alternating Current Stimulation: Towards Personalized Non-invasive Brain Stimulation for the Treatment of Psychiatric Illnesses

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Abstract

Purpose of Review This review introduces closed-loop transcranial alternating current stimulation (tACS), which has the potential to become an effective and safe treatment modality for psychiatric illnesses such as schizophrenia and depression.

Recent Findings The weak electric fields delivered to the brain by transcranial current stimulation interact in a synergistic manner with endogenous rhythmic brain activity patterns. As a result, the effect of stimulation on neuronal network dynamics is state dependent. Therefore, closed-loop paradigms that measure brain activity and apply targeted stimulation based on these measurements may allow effective modulation by targeted low-amplitude stimulation that is tuned to modulate the measured activity. Few initial studies of such closed-loop tACS have recently documented successful target engagement, mostly for applications that target specific activity patterns during sleep.

Summary Given the urgent need of novel therapeutic interventions for psychiatric disorders and the recent promising data from initial tACS clinical trials in psychiatry, we propose that closed-loop tACS deserves attention as a promising personalized medicine strategy in psychiatry.

Keywords Closed-loop · Feedback · Network oscillations · Depression · Schizophrenia

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Introduction

The application of weak electric current by non-invasive brain stimulation can modulate neuronal activity due to the highly non-linear nature of the brain, from the scale of individual ion channels up to large-scale networks. Despite significant gaps in our current mechanistic understanding of stimulation modalities such as transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS), the field has rapidly moved forward and used these stimulation modalities in numerous studies to probe the brain-behavior relationship with causal perturbations and as potential therapeutic modalities. Overall, efficacy remains an open question for several reasons, including the lack of neurophysiological confirmation of successful target engagement in many studies, the lack of appropriate double-blind, placebo-controlled trial designs, and the typically very small number of participants per study. In addition to these concerns about study design, it is also becoming clear that the stimulation dose needs to be contextualized by the brain network structure and dynamics at the time of stimulation since the weak perturbations of the membrane voltage caused by stimulation synergistically

interact with endogenous fluctuations in membrane voltage to generate the network-level effects of stimulation. Due to this state dependence of stimulation effects, a highly promising but underexplored strategy is to "close the loop" by adjusting the stimulation as a function of measured brain activity, also known as feedback control. Here, we explore the context and development of closed-loop tACS as well as its potential trajectory towards becoming an effective treatment for psychiatric illnesses associated with pathological brain oscillations, such as schizophrenia and depression.

First-Generation Transcranial Current Stimulation: Open-Loop

The application of weak electric current to the scalp for the modulation of brain activity has a long and convoluted history [1]. The last 20 years have brought an exciting resurgence of electrical non-invasive brain stimulation. Initial studies focused on the modulation of excitability in motor cortex [2], and the field quickly moved on to examine different waveforms and uncountable potential applications in cognitive and clinical neuroscience. Despite an explosion of pilot studies, there are only a very small number of larger studies with some failing to support the preregistered hypothesis [3••]. This adds to the growing concerns about the reproducibility and the quality of evidence for the wave of positive studies published over the last two decades [4]. More recently, a growing mechanistic understanding of how low-amplitude electric current modulates neuronal network activity has started to provide a foundation for the next generation of stimulation paradigms. Below, we introduce the most common types of non-invasive brain stimulation with low-amplitude current: transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), transcranial random noise stimulation (tRNS), and cranial electrotherapy stimulation (CES). The modalities of tDCS, tACS, and tRNS are often grouped together despite their potentially quite different mechanisms of action (Fig. 1a). In contrast, CES is often considered separate due to its relative lack of recent scientific investigations and its unique status in the USA due to a complex and evolving regulatory history such as receiving grandfathered FDA clearance at the introduction of medical device regulations in 1976 [5].

Transcranial Direct Current Stimulation

The stimulation waveform for tDCS is a constant current, which is applied by two or more electrodes to the scalp. tDCS stimulation amplitudes are typically 1 to 2 mA of current with stimulation durations that last up to an hour [6]. The electrode where the current flows into the brain is referred to as the anode, and the electrode where the current leaves the body is referred to as the cathode. In the simplest model, "anodal tDCS" increases cortical excitability and "cathodal tDCS" decreases cortical excitability [2, 7]. The small polarization of the neuronal membrane voltage by tDCS brings the neuron closer to the firing threshold at the soma and also modulates the processing of dendritic synaptic input, resulting in an altered input-output relationship [8]. These effects seem to persist at the end of the stimulation on the timescale of minutes to hours. Numerous studies have employed tDCS as a tool to increase or decrease excitability despite limited evidence that this principle holds true beyond specific circumstances in motor cortex [9]. While today's mechanistic understanding of tDCS is incomplete, current models focus on the role of BDNF-dependent synaptic plasticity [10] as well as other proposed factors including modulation of glial [11] and endothelial cells [12].

Transcranial Alternating Current Stimulation

In contrast to the constant current of tDCS, tACS applies a periodic, alternating stimulation waveform, typically a sinewave. Accordingly, the terms anode and cathode are not utilized since both electrodes alternatingly deliver inward and outward currents. Besides the stimulation amplitude, the frequency of the stimulation waveform is a critical, additional stimulation parameter in tACS. The simplest model for tACS is that it enhances the neural oscillation at the stimulation frequency, as demonstrated both in vitro [13, 14] and in vivo preclinical studies [15, 16, 17••]. A decade of computational and experimental work has resulted in a theory-grounded model of how tACS entrains neuronal oscillations that is described by the so-called Arnold tongue [17••, 18]. This phenomenon arises from dynamical systems theory showing that even infinitely small perturbations can modulate an oscillator if the frequency of the perturbation (i.e., stimulation) matches the endogenous frequency of the oscillator [19]. The challenge with tACS is the technical difficulty of measuring successful modulation of network activity due to stimulation artifacts that contaminate electroencephalography (EEG) and local field potential (LFP) measures of network activity [20]. In addition, the few studies that use repeat stimulation sessions over several days often show "outlasting" effects for which the underlying mechanisms remain mostly unknown [21, 22••]. Current hypotheses about the mechanism of persistent changes in network dynamics caused by tACS include both plasticity [23, 24] and state transitions enabled by intrinsic non-linearities at the network scale [25].

Transcranial Random Noise Stimulation

Perceived limitations of tACS include that it targets a specific oscillation that may (1) be poorly understood,

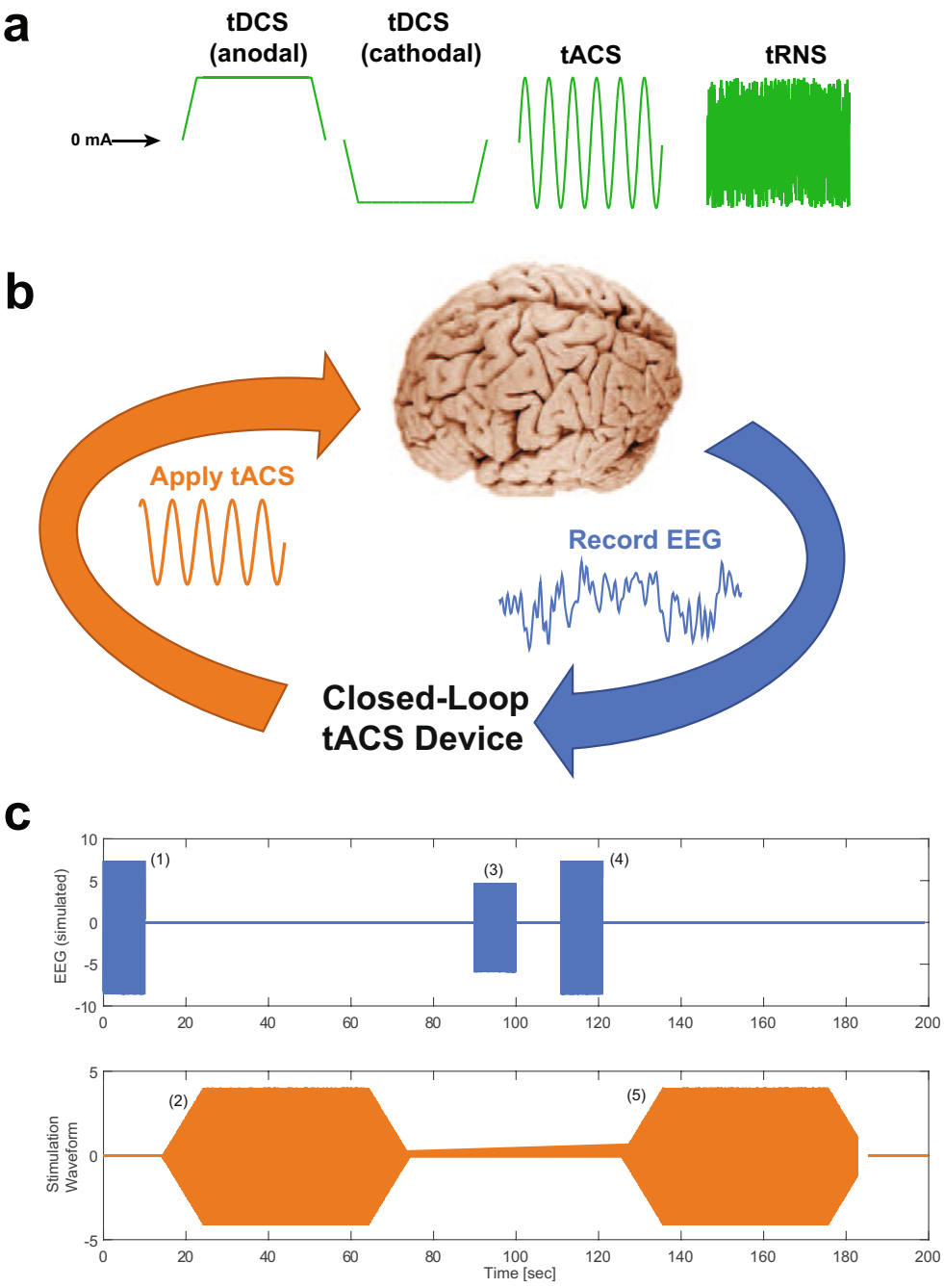

Fig. 1 **a** Stimulation waveforms for tDCS, tACS, and tRNS. **b** Closed-loop tACS measures brain activity in real time with EEG and applies a target tACS stimulation waveform as a function of the features detected in the EEG. In contrast to open-loop control, such feedback stimulation applies individualized stimulation since the stimulation current depends on the measured brain activity. **c** Sample recording from an initial test run of a prototype closed-loop tACS device. (1) Simulated EEG signal. (2) tACS waveform is applied in response to the measured EEG signal. (**3**) EEG signal is reduced in amplitude after stimulation, and thus, no further stimulation is applied. (4) EEG signal amplitude is increased again which triggers stimulation epoch (5)

(2) have a more complex waveform than a sinewave with a single peak frequency, and (3) be dynamic in nature. tRNS was developed in response to these concerns. This stimulation modality applies a broadband-filtered noise signal, under the guiding hypothesis that stochastic resonance will "unmask" and enhance oscillatory structure [26]. While direct evidence for this mechanism of action is currently lacking, there is a small but growing set of studies that suggest tRNS increases excitability of cortical circuits [27, 28].

Cranial Electrotherapy Stimulation

Cranial electrotherapy stimulation (CES) is fundamentally different from these other stimulation modalities due to its peculiar history with regulatory clearance in the USA. CES has its origin in historical research on "electro sleep" and delivers electrical pulses at different frequencies either to the forehead or the earlobes [5]. Adoption is limited despite its FDA clearance mostly due to the lack of convincing, large-scale clinical trials [29]. Today, the basic science around CES remains

limited as currently marketed devices use proprietary waveforms for which the mechanism of action remains unknown.

Next Generation of Transcranial Current Stimulation

Given the mixed results in the literature, it is not surprising that there is no FDA clearance for tDCS/tACS/tRNS for a clinical indication. More recent tDCS studies, which were carefully controlled (double-blind, placebo-controlled evaluation of successful study blind) and larger (there are at most a few studies with $N > 100$, but see for example with a carefully designed study with self-replication [30]), failed to provide evidence to reject the null hypothesis ("negative" studies), including a recent international clinical trial of tDCS for the treatment for depression [3••]. To move forward, a mechanistic understanding is required to enable the rational design of more effective stimulation paradigms [31, 32]. Synthesizing the current literature, the response to exactly the same stimulation paradigm is likely to differ quite a bit between individuals and will also fluctuate in a moment-to-moment fashion for a given individual as a function of state [33–35]. Thus, the "dose" of tDCS/tACS/tRNS needs to be contextualized by the physiology of the stimulated network. In order to advance these approaches and accelerate development as potential therapeutics, the stimulation waveform should be individualized and adaptive to maximize the effects of stimulation [32]. Since behavioral changes such as improvements in symptoms are typically not instantaneous, adaptation of the stimulation waveform needs to be guided by the measured response of the brain to the stimulation, such as an EEG signal acquired in between periods of stimulation [36].

Closed-Loop tACS

This principle of applying an input to a system that dynamically depends on the output of the system is in essence the fundamental principle of feedback in control engineering (Fig. 1b). It is important to note that the sophisticated mathematical strategies of control engineering cannot be easily translated to neuroscience and non-invasive brain stimulation since (1) the brain is highly non-linear and (2) there are no appropriate mathematical models of the brain that would allow the derivation of an optimal (or even just a reasonable) control algorithm. Rather, the development of feedback brain stimulation occurs in two discrete steps. First, the response of the brain to a given stimulation paradigm is determined (often termed "open loop"). Once a stimulation waveform that successfully modulates the target brain activity patterned is identified, this waveform is then used to build the feedback controller that applies the stimulation once the targeted activity pattern is detected. Current stimulation paradigms typically detect if oscillation amplitudes cross a certain threshold and apply stimulation in response (Fig. 1c). We performed a PUBMED search with the search string "("closed-loop" OR feedback) and tACS" on February 9, 2021. After excluding articles that did not study but only mentioned closed-loop tACS (12/24), review articles (1/24), and unrelated articles (5/24), we arrived at a list of six reports of closed-loop tACS and no clinical trials that investigated the clinical efficacy of closed-loop tACS. We then complemented the search with the personal literature database from one of the authors (FF) and identified one more study.

Most work in this space has focused on applying closed-loop tACS in sleep and memory. The first study of closed-loop tACS demonstrated the augmentation of sleep spindles with feedback tACS to investigate their causal role in memory consolidation [37••]. Sleep spindles are transient activity patterns generated by the thalamocortical system. In this study, each time a spindle was detected from a single EEG lead, stimulation (with a spindle waveform) was applied, which resulted in a selective increase of power in the sigma frequency band associated with spindles and a correlated increase in procedural memory consolidation. What remains unclear is to which extent the feedback aspect of the stimulation method was responsible for the effect since matched open-loop stimulation would be needed to more directly assess the increased efficacy by closed-loop stimulation. However, given the transient nature of spindles and the synergistic interaction with endogenous oscillation by tACS, it can be assumed that the targeting of spindles by closed-loop is of essence in such a paradigm. Closed-loop stimulation may be of therapeutic efficacy in patients with schizophrenia, which is associated with impaired sleep spindles [38]. Further studies were based on the seminal study that proposed target enhancement of slow oscillations for enhancing memory consolidation by periodic stimulation waveforms [39••]. A recent series of three studies reported an increase in long-term memory generalization [40, 41] and subjective sleep quality [42] by closed-loop tACS that applied stimulation matched in phase and frequency to enhance slow waves during deep sleep. Of note, the three publications of closed-loop tACS for modulation of slow oscillations during sleep are all reports from the same trial, which raises concerns about the generation of post hoc hypothesis and statistical issues related to repeated comparisons. In that study, the stimulation waveform was tuned in frequency and in phase to the EEG waveform.

Other early work with closed-loop tACS has focused on the effects of target engagement with a case study showing that the application of tACS in the gamma frequency band suppresses alpha oscillations since these two oscillation patterns are antagonistically organized [43]. In contrast, a recent study showed that application of short burst of tACS in the alpha frequency band suppressed

instead of enhanced alpha oscillations, independent of the phase alignment [44].

Similar approaches that detect the power of an oscillation band of interest and apply stimulation once a certain threshold is crossed have also been used for other brain stimulation modalities such as deep brain stimulation [45, 46]. Another approach is based on adjusting the stimulation as a function of other behavioral signals such as tremor measured by an accelerometer in patients with movement disorders [47•]. In this study, the stimulation waveform tracked the phase drifts of the tremor signal since a stable phase alignment between tremor and stimulation was hypothesized to cause destructive interference. However, successful target engagement at the level of neuronal oscillations for this approach remains to be investigated. Finally, numerous other types of closed-loop stimulation paradigms can be imagined; however, one of the key barriers to wider adoption of these approaches is the lack of easy-to-use technology for such stimulation paradigms to support the investigation of these research questions.

Closed-Loop tACS in Psychiatry

While off-the-shelf technology may still be under development, this has not prevented clinicians from taking note of recent research and developing an interest in the promise of closed-loop tACS as a potential therapeutic approach. In preparation of this manuscript, we spoke to 10 psychiatrists on a variety of topics, including future advances in the field that they are most excited about. These psychiatrists represent a wide range of practice care settings—from rural, private practice to outpatient clinics at major academic medical institutions—and of years of experience—from just graduate from a specialized neuromodulation fellowships to nearly three decades of clinical expertise. Given the several neuromodulation technologies that have FDA approval for the treatment of major depressive disorder (MDD) (CES, electroconvulsive therapy (ECT), and transcranial magnetic stimulation (TMS)), we broadly focused our conversations on the unmet need and potential future of care in MDD.

Across the board, the psychiatrists we spoke to indicated that they have a wide variety of pharmacotherapy tools at their disposal. Especially for MDD, there are numerous drug classes and varieties of approaches that they can step through for first- and second-line patient care. However, while there are detailed treatment guidelines and evidence-based approaches [48], many clinicians indicated that they want some way to be able to "listen into the brain" and have the brain "tell us what it needs." Further, despite the plethora of pharmacologic tools available, the clinicians we spoke to indicated that these treatments have a range of drawbacks including lack of efficacy, intolerable side effects, and decreasing efficacy over time. This is in alignment with (contentious) concerns about the potentially extremely low remission rate in the largest and defining study of depression treatments, the STAR*D trial [49].

Due to the high patient burden of unmanaged MDD, clinicians are enthusiastic about exploring treatment options, especially neurostimulation approaches. One clinician summarized their attitude as "it doesn't make much difference whether it is stimulation or medication – we just want our patients to get better." Eighty percent of the clinicians we spoke to mentioned that they felt current, FDA-approved neurostimulation technologies, specifically TMS and ECT, were effective; however, significant drawbacks prevented wider use. Lack of access, high logistical burden, resource intensiveness, and side-effect burden were cited as key barriers to utilizing these techniques more widely.

Given this current state of care, we asked these clinicians what they are most excited about in the field of psychiatry in the next 5 years. Many were strongly excited by the promise of closed-loop tACS to provide a precision medicine tool to psychiatry—provided that there was enough understanding of brain oscillations to develop and deploy this technology in a thoughtful way. Lack of side effects due to the low stimulation amplitude, treatment customized to individual patients, and a novel mechanism of action were viewed as key benefits to this approach. To date, studies utilizing tDCS/tACS/tRNS [6] have shown none of the side effects seen utilizing TMS (such as a low but non-zero seizure risk especially in combination with certain pharmacological agents, [50]) or ECT (such as short-term cognitive impairment, [51]), and there is no reason to suspect that closed-loop tACS would deviate from its open-loop predecessors in this regard. Closed-loop tACS could further accelerate the advancement of psychiatry to a precision medicine–focused field by providing psychiatrists with a personalized, evidence-based tool. Finally, the fact that this approach offers the potential for therapeutic benefit with a novel mechanism of action, without introducing yet another pharmacological agent that could further complicate the typical polypharmacy in treatment-resistant patients, is critical.

However, many clinicians that we spoke to highlighted that the promise of closed-loop tACS, while exciting and potentially revolutionary, remains just that, a promise. To capitalize on the promise and potential of this approach, researchers, clinicians, and companies developing stimulation technology will have to closely collaborate in order to successfully advance this approach that has the potential to revolutionize psychiatry.

Conclusion

Developing the next generation of tACS paradigms that provide closed-loop stimulation to modulate and restore neuronal oscillations represents a promising avenue towards a bright

future in psychiatry where individualized non-invasive brain stimulation restores brain function to alleviate the burden of psychiatric illnesses for which we currently only have inadequate treatments available. We thus urge the research community to focus on the further refinement and investigation of this promising brain stimulation modality. Although there have been no clinical trials of closed-loop tACS in psychiatry at this point, given the success of tACS (with no feedback) in recent trials, we anticipate that closed-loop tACS will lead to even more impressive therapeutic due to improved target engagement by closing the loop.

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Declarations

Conflict of Interest Flavio Frohlich has received research funding through grants from the National Institute of Mental Health (NIMH, grants R01MH101547 and R01MH111889) and from Pulvinar Neuro, LLC. Dr. Frohlich is also a paid consultant for Pulvinar Neuro, LCC. He also receives royalties from Pulvinar Neuro, LLC, for use of the XCSITE Stimulation Device, and is also listed as an inventor on the issued patent for Closed-Loop Brain Stimulation, which is licensed and for which he also receives royalties. Leah Townsend has received research funding through a grant from the NIMH (R43MH119872) and is the CEO and a shareholder of Pulvinar Neuro, LLC. The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Human and Animal Rights All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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- •• Of major importance

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