

Transcranial electrical stimulation in neurological disease

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Increased lifespan is one of society's greatest achievements, but this longevity increases the prevalence of diseases of aging, such as neurological disorders. Globally, neurological disorders are the leading cause of disability and the second leading cause of deaths (Feigin et al., 2019). Furthermore, these diseases affect people in low-, medium-, and high-income countries (Feigin et al., 2019). Current technology to modify neurological burden is scarce, which poses numerous challenges for healthcare, global policy, and economic stability (Feigin et al., 2019). To face these challenges, brain stimulation technology, such as transcranial electrical stimulation (TES), has displayed exciting potential. Antal et al. (2017) provide a detailed overview of the safety and application of TES. Commonly, electrodes are attached to the head and a weak current (e.g., 1–2 mA) is applied through the scalp, skull, and into the brain for 10–30 minutes to activate neurons (Antal et al., 2017). The technique is extremely safe with no serious adverse effects reported from thousands of sessions (Antal et al., 2017). The most common side effects are a tingling/itching sensation or redness at the stimulation site (Antal et al., 2017). However, these side effects can be minimized by reducing the electrode-skin impedance, slowly ramping up and ramping down TES, or using topical analgesics (Antal et al., 2017). The development of TES may repair neural dysfunction and stem the oncoming incidence of neurodegenerative disease.

Mechanisms of TES: TES is an overarching term that refers to multiple types of stimulation techniques. Paulus et al. (2016) provide a detailed review comparing the three main forms of transcranial electric stimulation: transcranial direct current stimulation (tDCS, **Figure 1A**), transcranial alternating current stimulation (tACS, **Figure 1B**), and transcranial random noise stimulation (tRNS, **Figure 1C**). The most studied TES technique is tDCS, where a sustained low-intensity current is applied (Paulus et al., 2016). Depending on the polarity of the current (i.e., anodal or cathodal), neuronal excitability can be increased or decreased, respectively (Paulus et al., 2016). In contrast to tDCS where the amplitude of current remains constant, the amplitude of current fluctuates in tACS (Paulus et al., 2016). These fluctuations in current amplitude entrain neuronal oscillatory rhythms (Paulus et al., 2016). The frequency of neuronal oscillations will depend on the frequency of alternating current oscillations (Paulus et al., 2016). When those oscillations are at random frequencies, the type of stimulation is considered tRNS (Paulus et al., 2016).

Animal models have indicated that tDCS alters membrane potential to increase long-term potentiation of neurons and increase synaptic plasticity through N-methyl-D-aspartate receptor-dependent processes (Paulus et al., 2016). Anodal tDCS (**Figure 1D**) increases neuronal excitability by depolarizing the cell bodies of pyramidal neurons (Paulus et al.,

2016). However, the membrane alterations are insufficient to directly induce neuronal firing, and the neurological effects of tDCS are due to an increased probability of firing (Paulus et al., 2016). Therefore, tDCS is often paired with a task to improve learning, and the best effects of tDCS have been reported when stimulation is performed during the task (Paulus et al., 2016). A technique to improve spatial localization is the use of high-definition TES (Paulus et al., 2016), which employs multiple cathodal electrodes around a singular anodal electrode (or vice versa).

In contrast to tDCS, tACS does not depolarize or hyperpolarize neurons, since the direction of current will alternate on each half-cycle (Paulus et al., 2016). Instead, the periodicity of tACS mimics neuronal oscillations to entrain biologically relevant rhythms (Paulus et al., 2016). The brain has multiple intrinsic brain frequencies [e.g., delta (0–4 Hz), theta (4–7 Hz), alpha (8–13 Hz), beta (13–30 Hz), gamma (30–80 Hz)], and entrainment of each will have differing effects on brain function (Klink et al., 2020). Amplitude, frequency, and phase of tACS are key considerations when determining the stimulation protocol (Paulus et al., 2016). A recent stimulation technique pioneered by Grossman et al. (2017) called temporal interference (**Figure 1**) utilizes high frequency (> 1 kHz) tACS to activate deep brain neurons. In temporal interference, two

high-frequency electric fields differ by a small frequency, Δf (Grossman et al., 2017). The two waves generate a temporally interfering envelope frequency that is equivalent to Δf (Grossman et al., 2017). High-frequency stimulation is ineffective since neurons are low pass filters, so only the lower frequency Δf envelope will stimulate neurons (Grossman et al., 2017). Directing the two waves so that the envelope overlaps with subcortical regions may induce oscillatory rhythms in these regions (Grossman et al., 2017). Future research into neuronal oscillations with tACS will provide an exciting new understanding of brain rhythms in network-scale neuronal signaling.

The utilization of tRNS is more recent than tDCS and tACS, so the mechanisms are less well studied. In general, tRNS uses a spectrum of oscillations ranging from 0.1 Hz to 640 Hz to increase neural activity (Paulus et al., 2016). Since the time constant of sodium channels in a neuron is longer than the stimulation frequencies, temporal summation occurs to aggregate multiple stimuli in a close temporal sequence (Paulus et al., 2016). This process is based on stochastic resonance, which indicates that noise can amplify a weak neuronal signal to increase overall firing (Paulus et al., 2016). Future research should investigate the effects of utilizing spectral envelopes of tRNS oscillations to increase the specificity induced by neural changes.

Currently, the major challenge preventing clinical implementation of TES is cortical targeting and stimulation protocols. Large longitudinal studies with robust stimulation protocols may help to identify reproducible best practices. Besides the direct effects of TES on neuronal activity, indirect mechanisms may be equally, if not more, involved in the effects of TES on brain function (Paulus et al.,

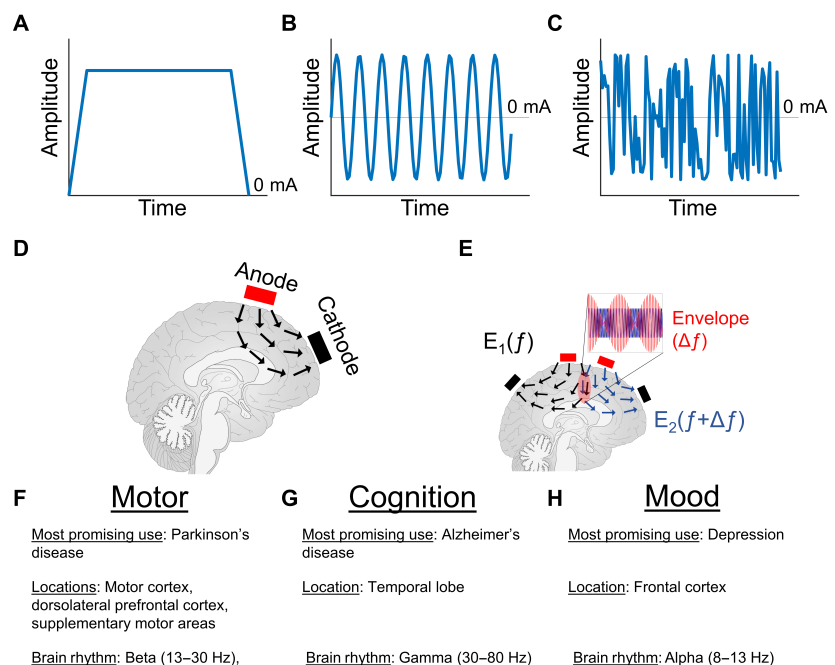


Figure 1 | Basics of transcranial electrical stimulation and most promising directions. Representative waveforms for (A) direct current, (B) alternating current, and (C) random noise stimulation. (D) Schematic of direct current flow in direct current transcranial electrical stimulation. (E) Schematic for temporal interference using two high-frequency currents that generate a beat frequency envelope. Current uses, locations of stimulation, and brain rhythms for (F) motor, (G) cognition, and (H) mood disorders. Δf : Difference frequency; E: electric field; f: frequency; Hz: hertz; mA: milliamp; tACS: transcranial alternating current stimulation; tDCS: transcranial direct current stimulation; TI: temporal interference; tRNS: transcranial random noise stimulation.

2016). These complementary mechanisms include glial function, vascular health, increased neurotrophic growth factors, and improved calcium signaling (Paulus et al., 2016). Due to the numerous potential permutations of TES protocols, understanding the most promising recent advancements in TES may pave a path for future research and impactful developments of TES technology in neurological disease.

Usage in neurological disease: Regulating dysfunctional brain networks has exciting potential to alleviate neurological illness. Due to both the breadth of neurological diseases and the variability of TES techniques, a variety of studies have been performed to investigate a range of TES applications in neurological disease. We will focus on three of the most promising applications: Parkinson's disease, Alzheimer's disease, and depression. We will also provide reference to more in-depth reviews in motor, cognition, and mood disorders for further understanding of this exciting new field.

Parkinson's disease may be one of the most promising applications of TES (Figure 1E). Deep brain stimulation is already an established and effective treatment for motor symptoms of Parkinson's disease (Perestelo-Pérez et al., 2014). TES may provide a non-invasive method to stimulate motor pathways. A meta-analysis in Parkinson's disease has indicated that tDCS improves freezing of gait, balance, gait speed, and upper limb function (Lee et al., 2019). Interestingly, combining motor cortex and frontal lobe stimulation seemed to have a large effect size, showing motor improvements after a single session (Lee et al., 2019). In Parkinson's disease, tACS in the beta band has been related to beneficial motor learning (Klink et al., 2020). Findings have also shown that previous identification of the pathological oscillations (i.e., beta or gamma) and subsequent personalized stimulation improved the effects of tACS (Del Felice et al., 2019). These findings highlight the potential to combine electroencephalography or functional magnetic resonance imaging with TES to optimize protocol settings and maximize benefit. Flöel et al. (2014) reviews tDCS in other movement disorders and suggests that stimulation of the motor cortex may improve motor learning after stroke and dystonia. TES may provide a treatment option for Parkinson's disease and movement disorders.

In Alzheimer's disease, stimulation of the temporal lobe has been beneficial for memory function (Flöel, 2014; Figure 1F). Furthermore, entrainment of gamma oscillations may improve clearance of amyloid and cognitive function in Alzheimer's disease (Martorell et al., 2019). This suggests gamma oscillations may modify disease progression and outcomes. Klink et al. (2020) review the differing frequency-specific effects of tACS on cognition. Briefly, delta stimulation relates to memory consolidation, theta stimulation relates to working memory, alpha stimulation relates to executive and attention, beta stimulation relates to working memory and executive function, and gamma stimulation relates to memory and information processing (Klink et al., 2020).

Many consumer TES devices claim to boost attention and focus, but little evidence suggests this is the case. Overall, early studies of TES in cognition are mixed, but promising. More work is necessary to characterize the parameter space with longer and more uniform study designs.

Possibly the closest application of TES to clinical utility is in depression. Electroconvulsive therapy and transcranial magnetic stimulation have been established therapies for depression (Nitsche et al., 2009). Therefore, TES may be a logical progression in using electromagnetic stimulation to treat depression. Almost all studies of tDCS in depression used anodal tDCS stimulation to the frontal cortex (Nitsche et al., 2009; Figure 1G). The most promising findings from tACS on depression have suggested that alpha (8–12 Hz) stimulation in frontal cortical areas may ameliorate depression (Elyamany et al., 2021). Elyamany et al. (2021) provide a detailed review of TES in other psychiatric disorders such as anxiety, post-traumatic stress disorder, and obsessive-compulsive disorder. Overall, the use of TES in mood disorders seems promising, either alone or in conjunction with other therapies.

Conclusions and future directions: Neurotechnology is a rapidly expanding field, and TES provides a simple, safe, cost-effective method to improve brain function and ameliorate neurological disorders. The abundance of rigorous, blinded, sham-controlled studies indicates that TES indeed alters neural function. However, the challenge over the coming years will be to fully explore the parameter space to yield optimized and reproducible results. Compliance, in general, is a major hurdle for the healthcare industry, so ease-of-use will be important for TES adoption. Fortunately, as technological literacy continues to increase in this ageing population, individuals are progressively willing to engage with neurotechnology that provides a perceived benefit. From our perspective, the most promising recent advancements in TES are temporal interference for non-invasive deep brain stimulation (Grossman et al., 2017), multisite stimulation to improve efficacy (Lee et al., 2019), and gamma oscillations for cognition (Martorell et al., 2019).

There are numerous exciting avenues for future TES development. (1) Compared to the more well-studied tDCS (Paulus et al., 2016), tACS and tRNS provide promising new avenues for TES research. (2) Identifying the optimal frequency of tACS for specific functions may improve outcomes. Future studies may also explore the ability to use tRNS within specific frequency bands to generate more specific cortical excitability. (3) Simultaneous stimulation and recording of neuronal activity may improve decision-making for location and frequency of stimulation and help elucidate the effects of TES. (4) Better understanding of the non-neuronal aspects (e.g., activation of microglia, increased blood flow, and improved astrocyte support) may further improve the ability of TES to increase brain longevity and slow neurodegeneration. (5) Finally, longitudinal studies are needed to understand the long-term effects of TES. Overall, a new understanding into stimulation protocols, related brain frequencies, electrode design, and mechanisms related to neurological health will continue to improve the effectiveness of TES. Within the next few years, TES may develop into an affordable, safe, and effective method to alter the neurological function and improve brain health.

Both authors declare that there is no conflict of interest in this paper. No conflicts of interest exist between Neurished and publication of this paper.

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Date of submission: July 29, 2021

Date of decision: September 27, 2021

Date of acceptance: November 5, 2021

Date of web publication: February 28, 2022

<https://doi.org/10.4103/1673-5374.335796>

How to cite this article: Brown GL, Brown MT (2022) Transcranial electrical stimulation in neurological disease. *Neural Regen Res* 17(10): 2221-2222.

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Open peer reviewer: Giovanni Assenza, *Università Campus Bio-Medico di Roma, Italy.*

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P-Reviewer: Assenza G; *C-Editors:* Zhao M, Zhao LJ, Qiu Y; *T-Editor:* Jia Y