

## PRIMER

# Entrainig neurons via noninvasive electric stimulation improves cognition

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**Abbreviations:** AC, alternating current; CSF, cerebrospinal fluid; EEG, electroencephalography; fMRI, functional magnetic resonance imaging; iEEG, intracranial electroencephalography; MEG,

## Abstract

Transcranial Alternating Current Stimulation (tACS) is a method that injects rhythmic currents into the human brain via electrodes attached to the scalp of a participant. This technique allows researchers to control naturally occurring brain rhythms and study their causal relevance for cognition. Recent findings, however, cast doubts on the effectiveness of tACS to stimulate the brain and its mode of action. Two new studies by Vieira and colleagues and Marchesotti and colleagues reported in the current issue report promising new results in showing that tACS can entrain single neuron activity and improve reading abilities in dyslexic individuals.

Cognitive neuroscientists nowadays have an arsenal of methods at their disposal to study the human brain. Methods such as scalp or intracranial electroencephalography (EEG/iEEG), magnetoencephalography (MEG), and functional magnetic resonance imaging (fMRI) record brain activity as it labors tirelessly in order to make sense of the world, enabling researchers to establish correlations between patterns of brain activity and behavior. While these studies have without doubt generated a wealth of knowledge, this approach limits neuroscientists to establishing correlational links, i.e., brain state X co-occurs with behavior Y. Notably, this is different from and considerably weaker than establishing a causal link, i.e., brain state X causes behavior Y. Establishing such causal relationships between brain patterns and behavior requires a method that directly changes the brain's activity and affects behavior accordingly.

One set of brain patterns that have often been assumed to have functional relevance for a wide variety of processes are neural oscillations [1,2]. Brain oscillations are usually categorized according to their frequency into one of many different bands, each associated with a multitude of processes within the brain. In order to draw any causal links between neural oscillations and behavioral processes, one has to somehow directly affect these neural oscillations. If one can both improve and deteriorate performance for a given task by manipulating these neural oscillations, one can make strong claims about its relevance for behavior.

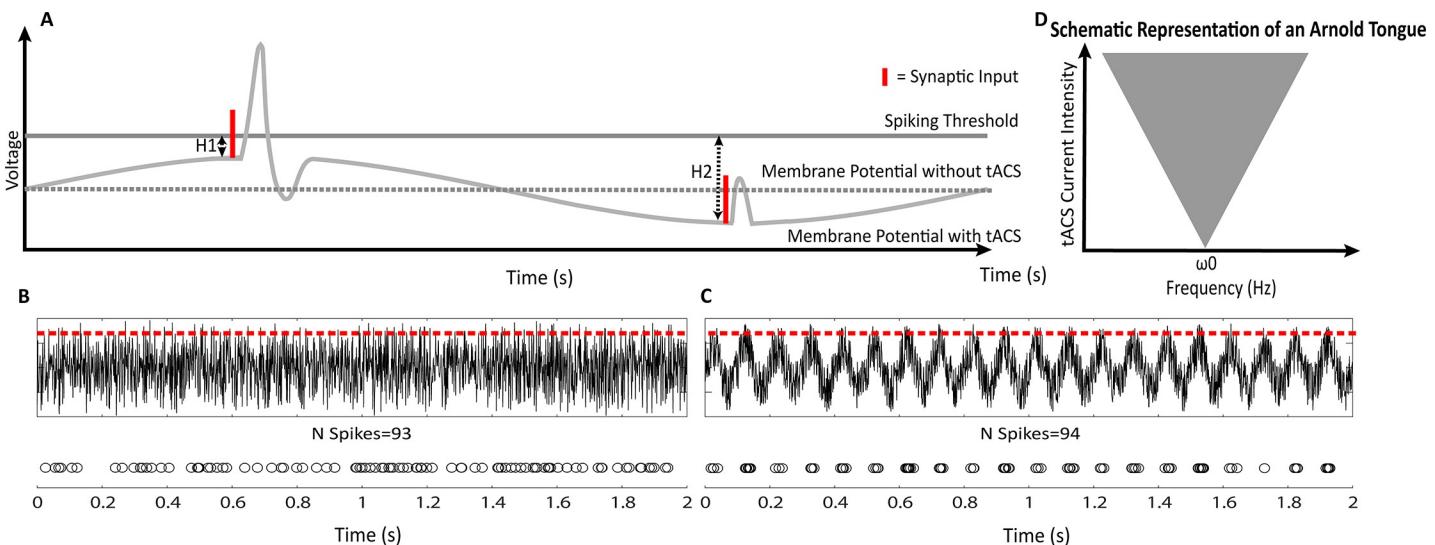
Transcranial Alternating Current Stimulation (tACS) is an electrical stimulation method that is often used with the aim of manipulating these brain oscillations directly [3–6]. This relatively simple procedure involves attaching at least two electrodes on the scalp, through which an alternating current (AC) is administered. Depending on the placement of the electrodes,

magnetoencephalography; tACS, transcranial Alternating Current Stimulation; TES, Transcranial Electrical Stimulation.

the currents' electrical field can affect the underlying neurons and bias their firing with sub-threshold polarity changes in the surrounding cerebrospinal fluid (CSF) in an oscillatory fashion (see Fig 1A). For example, if the surroundings of a neuron become more positively charged compared to its insides, the neuron will require a larger change in polarity to reach the threshold for an action potential, while a less positive charge will lower the threshold for an action potential. Since the direction of current flow is switched at a fixed rate, tACS biases the firing of the targeted neural population such that action potentials co-occur at certain time windows. In the human brain, co-occurrence of firing is evident in oscillatory activity, which is naturally present at many different rhythms [1]. TACS targets these natural brain oscillations in order to shift their phase to the phase of the applied stimulation, which is referred to as "entrainment" [7]. It is important to highlight that the stimulation resulting from tACS is merely assumed to affect the timing/synchronicity of neural firing but not directly affect the ongoing firing rate (see Fig 1B and 1C for an illustration). The window of how much one can affect a natural brain oscillation depends on both the field strength and frequency of the applied current. The lower the strength of the applied electric field, the smaller the window of frequencies one may entrain. This concept can be visualized with a diagram called the Arnold Tongue (see Fig 1D) [8,9].

Due to its potential in directly altering ongoing oscillations in the brain, tACS quickly became an attractive method in a variety of contexts. However, much of the early research pre-dated a deeper understanding of the method, resulting in tACS frequently being used suboptimally, leading to many null effects and failures to replicate positive results. This has frustrated the field and led many to question whether tACS can actually directly entrain neural activity [10–12]. One of the major criticisms resulted from an influential study applying tACS on human cadavers, which found that the electric currents commonly induced by Transcranial Electrical Stimulation (TES) were too weak to actually affect neural firing [13]. Further research on *in vivo* primate models and humans suggests that stimulation in the range of 1 mA peak-to-baseline (i.e., 2 mA peak-to-peak) can induce electrical fields ( $>0.2$  mV/mm) large enough to affect spike timing, in accordance with existing models of electrical conductivity in the brain [14,15]. This does cast doubt on many early studies using much lower stimulation intensities. It should, however, be noted that other factors, like electrode montage or distance to stimulation site, and not just intensity also play an important role. The above-cited studies are consistent with findings showing that tACS, applied in the range of 1 mA peak-to-baseline (i.e., 2 mA peak-to-peak), can affect spike timing of single neurons and neural adaptation in primates [16,17]. However, one problem with such intensities is that they also induce sensory effects (which is why earlier studies used lower intensities in the first place). This raises the additional concern that the mode of action of tACS is not through the current affecting neuronal populations in the brain directly but rather through its side effects, such as the somatosensory stimulation or stimulation of the retina, or indirect stimulation through cranial nerves [18–20]. A recent study by Asamoah and colleagues found that transcutaneous stimulation of peripheral nerves in the skin could entrain neurons in a rat model [21]. This finding was further supported by an additional experiment in the study in which anesthetic cream removed any tremor effects related to tACS in human participants, further linking somatosensory sensation and behavioral effects.

The study published in this issue by Vieira and colleagues can be seen as a direct response to the previously discussed research on the mechanisms of tACS [22]. The study further explores the mechanisms of tACS, by measuring neural firing in a primate model while systematically varying the parameter space, and its dependency on sensory stimulation. Vieira and colleagues report the effects of tACS on single neuron activity independent of somatosensory perception, supporting the idea that tACS can directly affect neural populations in certain



**Fig 1.** (A) Schematic Illustration of the commonly assumed mechanism of tACS. A typical sinusoidal cycle of tACS stimulation is illustrated, onto which action potentials of a hypothetical neuron are superimposed. At the peak of the wave, the current is assumed to raise the general excitability of neurons, pushing a given neuron closer to its firing threshold (solid black line). At the trough of the wave, the current pulls the neuron away from its firing threshold; therefore, the same synaptic input (visualized as a red line) might excite a given neuron sufficiently for an action potential in one state but not the other. (B–C) Simplified representation of the effects of sinusoidal stimulation on spike timings and spike rate as a result of an illustrative simulation. (B) Simulation of random noise, as a representation of ongoing activity. The red dotted line represents the threshold that has to be passed for an “action-potential.” Scatterplot below shows the amount of spikes and their timings. (C) Same as in B but with a sinusoidal on top of the random noise wave. While B and C have a very similar absolute amount of spikes, the distribution of spike-timings is random in B but is patterned according to the peaks of the sinusoid in C, just as one would expect from actual tACS. (D) Simplified schematic of an Arnold Tongue. The grey area indicates the frequency range that can be successfully entrained between two oscillators (in this case the tACS stimulation and the neural activity). With increasing amplitude ( $\epsilon$ ), a wider range of frequencies ( $\omega$ ) around the naturally occurring frequency ( $\omega_0$ ) in the brain can be entrained. tACS, transcranial Alternating Current Stimulation.

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conditions, not merely through indirect sensory means. One should note, however, that they were not able to completely disentangle direct effects of tACS from the possibility of affecting the populations indirectly through cranial nerves. However, not much research has focused on the relevance of cranial nerves on tACS, and this issue requires more attention by future research in general. Nevertheless, this study adds some compelling evidence, making the case for the capability of tACS to directly entrain neuronal populations in certain conditions.

Neural oscillations have been linked to a wide variety of phenomena, not only in the healthy brain but also in pathological cases [23,24]. Thus, research into the mechanisms of tACS helps researchers to fine-tune their parameters so that tACS may be used in a very targeted fashion to alter brain function, not just for research purposes but for clinical purposes as well. For example, neural oscillations have previously been implicated in language processing [25]. Thus, it would make sense that individuals with language processing issues, such as individuals suffering from dyslexia, might benefit from some kind of tACS stimulation. The study published in this issue by Marchesotti and colleagues provides an example for the potential of tACS to improve brain functioning in impaired individuals, as well as understanding ongoing processes in the brain [26]. Marchesotti and colleagues were able to improve reading performance in individuals suffering from dyslexia by applying targeted tACS at 30 Hz over the left auditory cortex, thus causally implicating the importance of oscillatory activity at 30 Hz for phonological processing. This important finding opens a potential avenue to aid individuals struggling with dyslexia and is a good example of how targeted tACS can be used for clinical treatments in addition to the research purposes.

Even though the mechanisms of tACS are still not completely understood, many studies are being performed in order for tACS to be used to the most of its potential. The study by Vieira and colleagues on a primate model has further explored the mechanism of tACS and its mode of action. Results from these types of studies into the mechanisms of tACS critically help tACS researchers in choosing the right parameters for their studies. In addition, such studies allow tACS to be used more effectively, by fine-tuning tACS to specific hypotheses, as demonstrated by Marchesotti and colleagues in work published in this issue [26]. Research efforts such as these will ultimately answer causal questions of brain oscillations and provide a means for novel treatments for a variety of disorders.

## References

1. Buzsaki G. *Rhythms of the Brain*. Oxford University Press; 2006 Aug 3.
2. Lakatos P, Gross J, Thut G. A new unifying account of the roles of neuronal entrainment. *Current Biology*. 2019 Sep 23; 29(18):R890–905. <https://doi.org/10.1016/j.cub.2019.07.075> PMID: 31550478
3. Priori A. Brain polarization in humans: a reappraisal of an old tool for prolonged non-invasive modulation of brain excitability. *Clinical neurophysiology*. 2003 Apr 1; 114(4):589–95. [https://doi.org/10.1016/s1388-2457\(02\)00437-6](https://doi.org/10.1016/s1388-2457(02)00437-6) PMID: 12686266
4. Antal A, Boros K, Poreisz C, Chaieb L, Terney D, Paulus W. Comparatively weak after-effects of transcranial alternating current stimulation (tACS) on cortical excitability in humans. *Brain stimulation*. 2008 Apr 1; 1(2):97–105. <https://doi.org/10.1016/j.brs.2007.10.001> PMID: 20633376
5. Paulus W. Transcranial electrical stimulation (tES–tDCS; tRNS, tACS) methods. *Neuropsychological rehabilitation*. 2011 Oct 1; 21(5):602–17. <https://doi.org/10.1080/09602011.2011.557292> PMID: 21819181
6. Thut G, Bergmann T, Fröhlich F, Soekadar S, Brittain J, Valero-Cabré A, et al. Guiding transcranial brain stimulation by EEG/MEG to interact with ongoing brain activity and associated functions: a position paper. *Clinical Neurophysiology*. 2017 May 1; 128(5):843–57. <https://doi.org/10.1016/j.clinph.2017.01.003> PMID: 28233641
7. Hanslmayr S, Axmacher N, Inman C. Modulating human memory via entrainment of brain oscillations. *Trends in neurosciences*. 2019 Jul 1; 42(7):485–99. <https://doi.org/10.1016/j.tins.2019.04.004> PMID: 31178076
8. Pikovsky A, Kurths J, Rosenblum M, Kurths J. *Synchronization: a universal concept in nonlinear sciences*. Cambridge university press; 2003 Apr 24.
9. Ali M, Sellers K, Fröhlich F. Transcranial alternating current stimulation modulates large-scale cortical network activity by network resonance. *Journal of Neuroscience*. 2013 Jul 3; 33(27):11262–75. <https://doi.org/10.1523/JNEUROSCI.5867-12.2013> PMID: 23825429
10. Asamoah B, Khatoun A, Mc Laughlin M. Analytical bias accounts for some of the reported effects of tACS on auditory perception. *Brain stimulation*. 2019 Jul 1; 12(4):1001–9. <https://doi.org/10.1016/j.brs.2019.03.011> PMID: 30930210
11. Haberbosch L, Schmidt S, Jooss A, Köhn A, Kozarzewski L, Rönnefarth M, et al. Rebound or entrainment? The influence of alternating current stimulation on individual alpha. *Frontiers in human neuroscience*. 2019 Feb 12; 13:43. <https://doi.org/10.3389/fnhum.2019.00043> PMID: 30809139
12. Lafon B, Henin S, Huang Y, Friedman D, Melloni L, Thesen T, et al. Low frequency transcranial electrical stimulation does not entrain sleep rhythms measured by human intracranial recordings. *Nature communications*. 2017 Oct 31; 8(1):1–4. <https://doi.org/10.1038/s41467-016-0009-6> PMID: 28232747
13. Vöröslakos M, Takeuchi Y, Brinyiczki K, Zombori T, Oliva A, Fernández-Ruiz A, et al. Direct effects of transcranial electric stimulation on brain circuits in rats and humans. *Nature communications*. 2018 Feb 2; 9(1):1–7. <https://doi.org/10.1038/s41467-017-02088-w> PMID: 29317637
14. Alekseichuk I, Falchier AY, Linn G, Xu T, Milham MP, Schroeder C, et al. Electric field dynamics in the brain during multi-electrode transcranial electric stimulation. *Nature communications*. 2019 Jun 12; 10(1):1–0. <https://doi.org/10.1038/s41467-018-07882-8> PMID: 30602773
15. Huang Y, Liu AA, Lafon B, Friedman D, Dayan M, Wang X, et al. Measurements and models of electric fields in the *in vivo* human brain during transcranial electric stimulation. *Elife*. 2017 Feb 7; 6:e18834. <https://doi.org/10.7554/elife.18834> PMID: 28169833
16. Kar K, Duijnhouwer J, Krekelberg B. Transcranial alternating current stimulation attenuates neuronal adaptation. *Journal of Neuroscience*. 2017 Mar 1; 37(9):2325–35. <https://doi.org/10.1523/JNEUROSCI.2266-16.2016> PMID: 28137971

17. Krause MR, Vieira PG, Csorba BA, Pilly PK, Pack CC. Transcranial alternating current stimulation entrains single-neuron activity in the primate brain. *Proceedings of the National Academy of Sciences*. 2019 Mar 19; 116(12):5747–55.
18. Kar K, Krekelberg B. Transcranial electrical stimulation over visual cortex evokes phosphenes with a retinal origin. *Journal of Neurophysiology*. 2012 Oct 15; 108(8):2173–8. <https://doi.org/10.1152/jn.00505.2012> PMID: 22855777
19. Liu A, Vöröslakos M, Kronberg G, Henin S, Krause MR, Huang Y, et al. Immediate neurophysiological effects of transcranial electrical stimulation. *Nature communications*. 2018 Nov 30; 9(1):1–2. <https://doi.org/10.1038/s41467-017-02088-w> PMID: 29317637
20. Schutter DJ. Cutaneous retinal activation and neural entrainment in transcranial alternating current stimulation: a systematic review. *Neuroimage*. 2016 Oct 15; 140:83–8. <https://doi.org/10.1016/j.neuroimage.2015.09.067> PMID: 26453929
21. Asamoah B, Khatoun A, Mc Laughlin M. tACS motor system effects can be caused by transcutaneous stimulation of peripheral nerves. *Nature communications*. 2019 Jan 17; 10(1):1–6. <https://doi.org/10.1038/s41467-018-07882-8> PMID: 30602773
22. Vieira PG, Krause MR, Pack CC. tACS entrains neural activity while somatosensory input is blocked. *PLoS Biol*. 2020 18(10): e3000834. <https://doi.org/10.1371/journal.pbio.3000834>
23. Uhlhaas PJ, Singer W. Abnormal neural oscillations and synchrony in schizophrenia. *Nature reviews neuroscience*. 2010 Feb; 11(2):100–13. <https://doi.org/10.1038/nrn2774> PMID: 20087360
24. Voytek B, Knight RT. Dynamic network communication as a unifying neural basis for cognition, development, aging, and disease. *Biological psychiatry*. 2015 Jun 15; 77(12):1089–97. <https://doi.org/10.1016/j.biopsych.2015.04.016> PMID: 26005114
25. Giraud AL, Poeppel D. Cortical oscillations and speech processing: emerging computational principles and operations. *Nature neuroscience*. 2012 Apr; 15(4):511. <https://doi.org/10.1038/nn.3063> PMID: 22426255
26. Marchesotti S, Nicolle J, Merlet I, Arnal LH, Donoghue JP, Giraud A-L. Selective enhancement of low-gamma activity by tACS improves phonemic processing and reading accuracy in dyslexia. *PLoS Biol*. 2020 18(9): e3000833. 3. <https://doi.org/10.1371/journal.pbio.3000833>