The New Modalities of Transcranial Electric Stimulation: tACS, tRNS, and Other Approaches

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Abstract

The most frequently used low-intensity transcranial electrical stimulation (tES) techniques are transcranial direct current (tDCS), alternating current (tACS), and random noise stimulation (tRNS). During tES, currents are applied with intensities ranging between 0.4 and 2 mA through the human scalp. It has been suggested that tACS interacts with cortical oscillations in a frequency-specific manner at single and using tRNS, at multiple frequencies. All techniques might affect homeostatic mechanisms or the signal-to-noise ratio in the brain. The aim of this review is to summarize basic aspects of tACS and tRNS, their possible neuronal mechanisms and clinical applications.

Keywords

Transcranial stimulation • Alternating current • Random noise • Brain oscillations

Introduction

Transcranial alternating current stimulation (tACS) is, to a certain extent, newer method than transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS) and better suited to noninvasively modulate brain oscillations (see [1, 2]). Technically, its application is similar to tDCS, although the concept with regard to the underlying mechanism is substantially different. During one half cycle of an AC oscillation, one electrode serves as anode and the other one as cathode and the current strength increases and decreases following a half sine wave. During the other half cycle, the pattern reverses ensuring the zero sums. Therefore, the membrane potential, on average, is not affected, but the depolarizing or hyperpolarizing effect of the cycle is assumed to be strong enough to modify neuronal activity and to induce online effects.

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Of course, it is possible to combine tACS with a DC offset, which is described later.

TACS can be classified as a form of tES, usually involving application of sinusoidal current across the scalp [3–5]. Also other pulse shapes, such as rectangular, may also be applied (not further dealt with here), although some authors suggested that tACS should not include rectangular or any other than non-sinusoidal waveforms. The possible physical spectrum may be indefinite in any case; the sinusoidal waveform may be biased, biphasic components can vary in amplitude and frequency, a combination of sinusoids could be used, and many more possibilities exist. With conventional intensities being limited to a maximum 2 mA peak-to-baseline [6], the applied intensities during tACS are at least two orders of magnitude less than the intensities intended to induce seizures as part of the therapeutic outcome and thus, are regarded safe.

Out of the indefinite spectrum some frequencies and intensities have been chosen to investigate the direction and the duration of the online effects and aftereffects. Most of these investigations used tACS frequencies in the physiologic EEG-detectable range, especially, when the intended outcome is to interact or influence these oscillations frequencies or measure them by EEG [5, 7–9]. TACS is applied in clinical research most relevant in Parkinson's disease (PD) [10]. Further insight in how brain oscillations are connected to cognitive functions causally will certainly predict more optimized stimulation parameters in the future. Furthermore, Higher frequencies then those in the EEG range, such as 140 Hz, may draw links to the frequencies used in deep brain stimulation (e.g., [6]).

Recent reviews cover quite extensively the existing literature (see [1, 2]), therefore here, we would like to focus on basic methodologic aspects and possible clinical applications.

tACS: Intrusion with Brain Oscillation

It is suggested by several animal and human studies that the mechanism of tACS is based on entrainment of brain oscillations. Modulation of active Purkinje cell activity by AC fields was shown by Chan and Nicholson in 1988 [11]. Later Francis and colleagues [12] demonstrated that electric pulses of 140 μV/mm root mean square or 295 μV/mm peak amplitude were sufficient to increase the firing rate of single neurons in the rat hippocampal slices at the lower end of intensities. Nevertheless, in this study pulsed stimulation was used and not the classical sinusoidal tACS.

Entrainment of neuronal oscillations by weak electrical AC stimulation was shown first by Deans and colleagues for induced gamma frequencies [13] and at the same time at the single neuron spiking level by Radman et al. [14]. Later, Fröhlich, Ozen and Reato extended the existing concepts for slow-waves and gamma oscillations. Coupling constants, as defined how many mV of a neurons membrane is polarized per V/m electric field, were differed: the field gradient varied between 0.2 and 1 mV/mm, which might be due to the different experimental setups and animal types. Ozen and colleagues [15] attached stainless steel wires to the skull of anesthetized rats, stimulated them electrically with AC and simultaneously recorded intracranial activity. Here, an entrainment of ongoing neuronal activity at frequencies mimicking the frequency of cortical slow oscillations in the frequency range of 0.8–1.7 Hz was found in many cortical areas. Voltage gradients of 1 mV/mm in the extracellular space were sufficient to affect discharge probability of neurons. At the low intensity end with sinusoidal stimulation Reato and colleagues [16] performed electrical stimulation experiments in slices of rat hippocampus and also simulations on neuronal networks. Both experiments revealed a threshold of 0.2 mV/mm before an AC was able to modulate ongoing neural activity. Fröhlich and McCormick [17] applied AC fields to the cortical slices of ferrets. They were able to demonstrate that AC fields at 0.5 mV/mm were sufficient to modulate the ongoing neural activity.

Nevertheless, the results of the animal studies might not be directly translated to human experiments. Indeed, computer simulations of the current flow during tDCS using models of the human head have revealed that a significant amount of

the current may be shunted by the well conducting skin (~90 %), while less current reaches the brain [18]. Furthermore, at the case of tACS the frequency response of each type of conducting element between the electrodes and the brain should also be taken into account [19].

Modulating the Activity of the Human Brain Using tACS

Different outreads have been used to measure cortical modulation by tACS. An enhancement of the EEG alpha amplitude was seen at the posterior part of the brain after 10 Hz tACS [7] with aftereffects for 30 min after 10 min of stimulation [20]. The elevation of EEG amplitudes can correlate with behavioral outcomes: e.g., amplification of gamma oscillations (30–80 Hz) with 40 Hz tACS during sleep led to the induction of lucid dreaming [21]. Linear increases in stimulation intensity may have nonlinear effects on the affected neural tissue and the physiological or behavioral consequences with lower intensities inducing inhibition and higher intensities excitation [6].

The frequency of the brain oscillations can also be modulated by tACS. Animal studies have demonstrated that stimulating cortical tissue at a stimulation frequency below the frequency of intrinsic oscillations can slow down the brain oscillations, and stimulating at a frequency above the intrinsic oscillations can speeded it up [17]. In human studies a similar effect was observed as well. Helfrich and coworkers [7] found an increase of the EEG alpha peak during 10 Hz tACS over the visual cortex. However, we should note that entraining oscillations does not only affect oscillations at the frequency of stimulation, but also at harmonic multiples as well as subharmonics. Furthermore, certain frequencies can interact with others referred to as cross-frequency coupling [22, 23]. Therefore, it has to be assumed that entraining one frequency may affect other frequencies. Same argument states with regard to the anatomical location of the effect: long-range coupling of cortical oscillations will most certainly trigger changes within the whole functional network. Thus, modulation of brain oscillations by tACS will not be a linear process and the effect may not be limited to the given frequency or area of stimulation.

Modulation of the phase of the brain oscillations can also have physiological and behavioral relevance. When using more than two electrodes, it is possible to manipulate the phase of the stimulation, which refers to the angle of the sinusoid relative to different electrodes, enabling anti-phase or in-phase stimulation. Correspondingly, brain areas that exposed to the similar conditions by in-phase stimulation are expected to facilitate their communications with each other. For example changing the inter-hemispheric phase-coherence in the gamma range via 40 Hz tACS have led to altered perceptions of ambiguous motion stimuli [24–26]. In the auditory cortex using 10 Hz tACS resulted in altered perception of a near-threshold auditory stimulus [27]. Stimulating the left frontal and parietal cortex by 6 Hz tACS in phase, cognitive performance in a delayed letter discrimination task was improved, when stimulating out of phase it was worsened [28].

Using tACS on Another Way: tRNS

Transcranial random noise stimulation (tRNS) was developed with the intent to desynchronize pathological cortical rhythms [29]. The technical application of tRNS can be adapted from tDCS and tACS, such that the electrode-montages and the applied paradigms are the same or very similar. Here, the stimulation is conventional biphasic like at the case of tACS, with various forms of noise. In typical examples, during tRNS a white noise in a frequency spectrum between 0.1 and 640 Hz (full spectrum) or 101–640 Hz (high frequency stimulation) can be applied. During one embodiment of "random noise" stimulation, the probability function of the stimulation follows a Gaussian or bell-shaped curve with zero mean and a variance, where 99 % of all generated current levels were between ± 1 mA (when 1 mA stimulation intensity is used). It was observed that filtering of the high-frequency subdivision between 100 and 640 Hz of the whole tRNS spectrum is functionally

responsible for alteration of excitability, at least in the motor cortex [29].

The physiological mechanisms of tRNS are largely unexplored due to missing animal studies. Although higher frequencies (e.g., 140 Hz) have been shown to modulate brain activity, at least in the motor cortex, the neuronal membrane acts as a low-pass filter, and therefore, high frequencies that are applied during tRNS are supposed to polarize neurons only by a very small amount. Deans and colleagues [13] measured the polarization of neurons during AC stimulation and estimated the coupling constant between electric field and induced polarization (mV per V/m applied). They found that 100Hz AC stimulation gave a coupling constant of 0.050 mV per V/m. Therefore, 1 V/m in the brain at 100Hz can polarize a neuron by only 50 μV. This intensity is too small to modulate the single neuron activity. One possibility can be that many synaptically connected active neurons can provide an amplification mechanism of the basic stimulation effect [16, 17].

One potential online effect of tRNS might be associated with repetitive opening of Na+ channels, observed in rat hippocampal slices during the application of AC stimulation [30]. In humans a recent pilot study the Na+ channel blocker carbamazepine showed a tendency towards inhibiting the activity of the motor cortex post stimulation [31].

The effects of tRNS might be based on other mechanisms, it was suggested that tRNS may increase synchronization of neural firing through amplification of subthreshold oscillatory activity, which in turn reduces the amount of endogenous noise (e.g., [32]). However, it is not clear, how this process can induce long-term, neuroplastic-like changes in the human brain. For example Cappelletti and colleagues using the repeated bilateral parietal stimulation showed the increased numerosity discrimination ability [33] that last for several weeks. Another study reported that bifrontal application of tRNS for 5 days enhanced the speed of both calculation- and memory-recall-based arithmetic learning [34]. Six months later the behavioral effects in the stimulated group relative to sham controls were still present.

Other Types of Oscillatory tES: Oscillating Transcranial Direct Current Stimulation (o-DCS)

Oscillatory tDCS (o-tDCS, also abbreviated as so-tDCS or ts-DCS) is a form of tES using DC stimulation where waveform is typically monophasic square or monophasic sinusoidal wave stimulation. Slow oscillatory tDCS (so-tDCS) conventionally refers to a signal with a frequency below 1 Hz [35]. Transcranial Sinusoidal Direct Current Stimulation (ts-DCS) is a form of o-tDCS where the waveform is a monophasic, biased sinusoid. so-tDCS may also be used to describe protocols with sinusoids when the frequency is low [35, 36]. ts-DCS frequencies and intensities are similar to those used in tACS [3]. The duty cycle of o-tDCS and its derivatives can be varied (e.g., [36] 5 intervals with 1 min gap).

These forms of stimulation are not so frequently used in the research than the conventional tACS and many times they are described as tDCS. However, the distinction between o-tDCS and the conventional tDCS applied intermittently and repeatedly (repetitive tDCS: e.g., 15 s on/off tDCS, from [37]) is, that tDCS is probably effective during the sustained phase of the stimulation while o-tDCS is anticipated to produce changes during the alteration phase of the current when the current flow is nonstatic.

Clinical Applications

Many studies have indicated that both tACS and tRNS are effective at modulating brain activity and result in behavioral effects in human subjects; nevertheless, they are rarely applied in patient populations.

Tinnitus has been attributed to reduced activity in the alpha range in the auditory cortex [38]. For the reduction of the symptoms of tinnitus it has been shown that low frequency tRNS (0.1–100 Hz) was more effective than either tDCS or interestingly, tACS using the individual alpha frequency [39]. Another study reported a significantly more pronounced reduction in loudness and distress in pure tone tinnitus compared to

narrow band noise tinnitus when high frequency tRNS was applied [40]. Based on these results, tRNS over the auditory cortex is a promising treatment option for different types of tinnitus, nevertheless, there a clear mechanistic explanation for the different results obtained with different types of tRNS is still not exist. With regard to other disorders, in neuropathic pain one patient out of four responded to tRNS applied over the motor cortex [41].

tACS is probably suited to treat disorders, which are characterized by distorted brain oscillations, by restoring to their original function. It was found that tACS has the potential as a therapeutic application in PD. Oscillatory activity, which guides the motor cortex, originating from the globus pallidus internus is increased in patients suffering from tremor. Brittain and coworkers [10] applied tACS over the motor cortex in patients diagnosed with tremor-dominant PD. tACS was most effective at the individual tremor frequency for inducing cortical phase cancellation, presumably due to suppression of the resting tremor amplitude. This study used a closed loop stimulation setup: tremor frequency was measured online and the motor cortex stimulation parameters were adjusted according to the measured activity. It was proposed that closed-loop individually adjusted stimulation can considerably surpass the traditional approach.

In another study Krause and colleagues [42] studied the effects of 10 and 20 Hz as well as sham tACS in PD patients and healthy controls. The application of 20 Hz tACS reduced the cortico-muscular coherence amplitude in the beta band upon isometric contraction during fast finger tapping in PD patients, but not in healthy control subjects. These results suggest that tACS could probably entrain cortical oscillation in PD patients and opening a promising field in the therapy of movement disorders.

Repetitive transorbital alternating current stimulation (rtACS) as a tool for visual rehabilitation also demonstrated promising results. During this intervention, electrodes are positioned near the eye aiming to inject current to the eyeball, stimulating the retina. The active electrodes include two super-orbital electrodes, four active electrodes placed above and below the eye and one return electrode is positioned on the right upper arm or right shoulder [43, 44]. rtACS has been proposed to induce vision restoration by activating residual visual functions in patients with damage to the retina, optic nerve, or visual system.

There are other possibilities, e.g., epilepsy would be another disorder that can feasibly be treated by tACS. It was found that in epileptic patients shortly before a seizure an increased synchronization of gamma band oscillations occur [45]. Thus, multichannel tACS may induce enough desynchronization to restrain an upcoming epileptic event.

Bifrontal oscillatory currents in the theta range enhanced functional connectivity between the prefrontal components of working memory and retrospective monitoring in humans [46]. These results support the feasibility of utilizing tACS to treat theta-rhythm functional disconnectivity and related cognitive impairments, e.g., in schizophrenia. Nevertheless, there are no published clinical trials on this field yet.

Conclusions

Not many tACS studies exist so far, thus experience with the application of this type of stimulation is still limited. The so far insufficient duration of the aftereffects (except 140 Hz tACS) might be increased using longer stimulation duration or repetitive stimulation during days or weeks, or with optimized stimulation protocols, such as an intermittent short stimulation paradigm (8 s stimulation and 8 s pause) [47]. Another important question would be to clarify the exact neuronal mechanisms underlying the tACS effects. Many studies suggest that tACS can entrain and enhance cortical oscillations (see above), however, not excluding the possibility that tACS induces short term plasticity rather than entrainment [47].

Compared to tDCS, tACS and tRNS have a better blinding potential with regard to the cutaneous sensations, such as itching, tingling or burning [48]. Furthermore, absence of the polarity effect, typical for tDCS [49], and presence of

the oscillatory phase provide an additional degree of freedom during the experimental design. Nevertheless, phosphene perception during tACS in a wide frequency range (6–70 Hz), might affect the execution of the task and the understanding of results (e.g., by inducing shifts in arousal, compared to sham stimulation).

Due to the above-mentioned multiplicity of tACS parameters and paradigm, tACS experiments requires fixation of more factors, compared to tDCS. Also, clarification of physiological characteristics, e.g., which oscillations that associated with a given motor or cognitive process are going to be modified in a healthy or patient population, may optimize effects. It should be clear whether the frequency, amplitude, or phase would be modulated. Application of the multi-electrode arrays together with the electric field modeling allows for targeting more complex neuronal assemblies, such as the coherence between two or more brain regions. Control stimulation frequencies next to the sham stimulation or the stimulation of another brain area not being involved in a given task will improve significance of the results. Finally, the importance of the double-blinded placebo-controlled experimental design should not be underestimated.

tACS and tRNS supplement tDCS in research and in clinical practice. Development of hypothesis-driven approaches based on brain oscillations and behavior are expected to provide another perspective that can bring major progress in the near future.

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References

1. Fröhlich F. Experiments and models of cortical oscillations as a target for noninvasive brain stimulation. Prog Brain Res. 2015;222:41–73. doi:10.1016/bs.pbr.2015.07.025.
2. Fröhlich F, Sellers KK, Cordle AL. Targeting the neurophysiology of cognitive systems with transcranial alternating current stimulation. Expert Rev Neurother. 2015;15(2):145–67. doi:10.1586/14737175.2015.992782.
3. 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 Stimul. 2008;1(2):97–105. doi:10.1016/j.brs.2007.10.001.
4. Kar K, Krekelberg B. Transcranial alternating current stimulation attenuates visual motion adaptation. J Neurosci. 2014;34(21):7334–40. doi:10.1523/JNEUROSCI.5248-13.2014.
5. Mehta AR, Brittain J-S, Brown P. The selective influence of rhythmic cortical versus cerebellar transcranial stimulation on human physiological tremor. J Neurosci. 2014;34(22):7501–8. doi:10.1523/JNEUROSCI.0510-14.2014.
6. Moliadze V, Atalay D, Antal A, Paulus W. Close to threshold transcranial electrical stimulation preferentially activates inhibitory networks before switching to excitation with higher intensities. Brain Stimul. 2012;5(4):505–11. doi:10.1016/j.brs.2011.11.004.
7. Helfrich RF, Schneider TR, Rach S, Trautmann-Lengsfeld SA, Engel AK, Herrmann CS. Entrainment of brain oscillations by transcranial alternating current stimulation. Curr Biol. 2014;24(3):333–9. doi:10.1016/j.cub.2013.12.041.
8. Jaušovec N, Jaušovec K. Increasing working memory capacity with theta transcranial alternating current stimulation (tACS). Biol Psychol. 2014;96:42–7. doi:10.1016/j.biopsycho.2013.11.006.
9. Reato D, Rahman A, Bikson M, Parra L. Effects of weak transcranial alternating current stimulation on brain activity—a review of known mechanisms from animal studies. Human Neurosci. 2013;7(October):1–8. doi:10.3389/fnhum.2013.00687.
10. Brittain J-S, Probert-Smith P, Aziz T, Brown P. Tremor suppression by rhythmic transcranial current stimulation. Curr Biol. 2013;23(5):436–40. doi:10.1016/j.cub.2013.01.068.
11. Chan CY, Hounsgaard J, Nicholson C. Effects of electric fields on transmembrane potential and excitability of turtle cerebellar Purkinje cells in vitro. J Physiol. 1988;402:751–71.
12. Francis JT, Gluckman BJ, Schiff SJ. Sensitivity of neurons to weak electric fields. J Neurosci. 2003;23(19):7255–61.
13. Deans JK, Powell AD, Jefferys JGR. Sensitivity of coherent oscillations in rat hippocampus to AC electric fields. J Physiol. 2007;583(2):555–65. doi:10.1113/jphysiol.2007.137711.
14. Radman T, Su Y, An JH, Parra LC, Bikson M. Spike timing amplifies the effect of electric fields on neurons: implications for endogenous field effects. J Neurosci. 2007;27(11):3030–6. doi:10.1523/JNEUROSCI.0095-07.2007.
15. Ozen S, Sirota A, Belluscio M, Anastassiou C, Stark E, Koch C. Transcranial electric stimulation entrains cortical neuronal populations in rats. J Neurosci. 2010;30(34):11476–85. doi:10.1523/JNEUROSCI.5252-09.2010.
16. Reato D, Rahman A, Bikson M, Parra L. Low-intensity electrical stimulation affects network dynamics by modulating population rate and spike timing. J Neurosci. 2010;30(45):15067–79. doi:10.1523/JNEUROSCI.2059-10.2010.

17. Frohlich F, McCormick D. Endogenous electric fields may guide neocortical network activity. Neuron. 2010;67:129–43. doi:10.1016/j.neuron.2010.06.005.
18. Holdefer RN, Sadleir R, Russell MJ. Predicted current densities in the brain during transcranial electrical stimulation. Clin Neurophysiol. 2006;117(6):1388–97. doi:10.1016/j.clinph.2006.02.020.
19. Akhtari M, Bryant HC, Emin D, Merrifield W, Mamelak N, Sutherling WW, et al. A model for frequency dependence of conductivities of the live human skull. Brain Topogr. 2003;16(1):39–55.
20. Neuling T, Rach S, Herrmann C. Orchestrating neuronal networks: sustained after-effects of transcranial alternating current stimulation depend upon brain states. Front Hum Neurosci. 2013;7(April):161. doi:10.3389/fnhum.2013.00161.
21. Voss U, Holzmann R, Hobson A, Paulus W, Koppehele-Gossel J, Klimke A, et al. Induction of self awareness in dreams through frontal low current stimulation of gamma activity. Nat Neurosci. 2014;17(6):810–2. doi:10.1038/nn.3719.
22. Canolty R, Edwards E, Dalal S, Soltani M, Nagarajan S, Kirsch H, et al. High gamma power is phase-locked to theta oscillations in human neocortex. Sci Rep. 2006;313(September):1626–8. doi:10.1126/science.1128115.
23. Jensen O, Colgin L. Cross-frequency coupling between neuronal oscillations. Trends Cogn Sci. 2007;11(7):267–9. doi:10.1016/j.tics.2007.05.003.
24. Cabral-Calderin Y, Schmidt-Samoa C, Wilke M. Rhythmic gamma stimulation affects bistable perception. J Cogn Neurosci. 2015;27(7):1298–307. doi:10.1162/jocn_a_00781.
25. Helfrich RF, Knepper H, Nolte G, Strüber D, Rach S, Herrmann CS, et al. Selective modulation of interhemispheric functional connectivity by HD-tACS shapes perception. PLoS Biol. 2014;12(12), e1002031. doi:10.1371/journal.pbio.1002031.
26. Strüber D, Rach S, Trautmann-Lengsfeld SA, Engel AK, Herrmann CS. Antiphasic 40 Hz oscillatory current stimulation affects bistable motion perception. Brain Topogr. 2014;27(1):158–71. doi:10.1007/s10548-013-0294-x.
27. Neuling T, Rach S, Wagner S, Wolters CH, Herrmann CS. Good vibrations: oscillatory phase shapes perception. Neuroimage. 2012;63(2):771–8. doi:10.1016/j.neuroimage.2012.07.024.
28. Polania R, Nitsche M, Korman C, Batsikadze G, Paulus W. The importance of timing in segregated theta phase-coupling for cognitive performance. Curr Biol. 2012;22(14):1314–8. doi:10.1016/j.cub.2012.05.021.
29. Terney D, Chaieb L, Moliadze V, Antal A, Paulus W. Increasing human brain excitability by transcranial high-frequency random noise stimulation. J Neurosci. 2008;28(52):14147–55. doi:10.1523/JNEUROSCI.4248-08.2008.
30. Schoen I, Fromherz P. Extracellular stimulation of mammalian neurons through repetitive activation of Na+ channels by weak capacitive currents on a silicon chip. J Neurophysiol. 2008;100(1):346–57. doi:10.1152/jn.90287.2008.
31. Chaieb L, Antal A, Paulus W. Transcranial random noise stimulation-induced plasticity is NMDA-receptor independent but sodium-channel blocker and benzodiazepines sensitive. Front Neurosci. 2015;9(April):1–9. doi:10.3389/fnins.2015.00125.
32. Miniussi C, Harris JA, Ruzzoli M. Modelling non-invasive brain stimulation in cognitive neuroscience. Neurosci Biobeh Rev. 2013;37(8):1702–12. doi:10.1016/j.neubiorev.2013.06.014.
33. Cappelletti M, Gessaroli E, Hithersay R, Mitolo M, Didino D, Kanai R, et al. Transfer of cognitive training across magnitude dimensions achieved with concurrent brain stimulation of the parietal lobe. J Neurosci. 2013;33(37):14899–907. doi:10.1523/JNEUROSCI.1692-13.2013.
34. Snowball A, Tachtsidis I, Popescu T, Thompson J, Delazer M, Zamarian L, et al. Long-term enhancement of brain function and cognition using cognitive training and brain stimulation. Curr Biol. 2013;23(11):987–92. doi:10.1016/j.cub.2013.04.045.
35. Groppa S, Bergmann TO, Siems C, Mölle M, Marshall L, Siebner HR. Slow-oscillatory transcranial direct current stimulation can induce bidirectional shifts in motor cortical excitability in awake humans. Neuroscience. 2010;166(4):1219–25. doi:10.1016/j.neuroscience.2010.01.019.
36. Eggert T, Dorn H, Sauter C, Nitsche M a, Bajbouj M, Danker-Hopfe H. No effects of slow oscillatory transcranial direct current stimulation (tDCS) on sleep-dependent memory consolidation in healthy elderly subjects. Brain Stimul. 2013;6(6):938–45. doi:10.1016/j.brs.2013.05.006.
37. Marshall L, Mölle M, Hallschmid M, Born J. Transcranial direct current stimulation during sleep improves declarative memory. J Neurosci. 2004;24(44):9985–92. doi:10.1523/JNEUROSCI.2725-04.2004.
38. Weisz N, Moratti S, Meinzer M, Dohrmann K, Elbert T. Tinnitus perception and distress is related to abnormal spontaneous brain activity as measured by magnetoencephalography. PLoS Med. 2005;2(6), e153. doi:10.1371/journal.pmed.0020153.
39. Vanneste S, Fregni F, De Ridder D. Head-to-head comparison of transcranial random noise stimulation, transcranial ac stimulation, and transcranial DC stimulation for tinnitus. Front Psychiatry. 2013;4:31–3. doi:10.3389/fpsyt.2013.00158.
40. Joos K, De Ridder D, Vanneste S. The differential effect of low-versus high-frequency random noise stimulation in the treatment of tinnitus. Exp Brain Res. 2015;233(5):1433–40. doi:10.1007/s00221-015-4217-9.
41. Alm P, Dreimanis K. Neuropathic pain: transcranial electric motor cortex stimulation using high frequency random noise. Case report of a novel treatment. J Pain Res. 2013;6:479. doi:10.2147/JPR.S44648.
42. Krause V, Wach C, Südmeyer M, Ferrea S, Schnitzler A, Pollok B. Cortico-muscular coupling and motor performance are modulated by 20 Hz transcranial alternating current stimulation (tACS) in Parkinson's disease. Front Hum Neurosci. 2013;7:928. doi:10.3389/fnhum.2013.00928.

43. Fedorov A, Jobke S, Bersnev V, Chibisova A, Chibisova Y, Gall C, et al. Restoration of vision after optic nerve lesions with noninvasive transorbital alternating current stimulation: a clinical observational study. Brain Stimul. 2011;4(4):189–201. doi:10.1016/j.brs.2011.07.007.
44. Gall C, Fedorov AB, Ernst L, Borrmann A, Sabel B a. Repetitive transorbital alternating current stimulation in optic neuropathy. NeuroRehabilitation. 2010;27:335–41. doi:10.3233/NRE-2010-0617.
45. Herrmann CS, Demiralp T. Human EEG gamma oscillations in neuropsychiatric disorders. Clin Neurophysiol. 2005;116(12):2719–33. doi:10.1016/j.clinph.2005.07.007.
46. Meiron O, Lavidor M. Prefrontal oscillatory stimulation modulates access to cognitive control references in retrospective metacognitive commentary. Clin Neurophysiol. 2014;125(1):77–82. doi:10.1016/j.clinph.2013.06.013.
47. Vossen A, Gross J, Thut G. Alpha power increase after transcranial alternating current stimulation at alpha frequency (α-tACS) reflects plastic changes rather than entrainment. Brain Stimul. 2015;8(3):499–508. doi:10.1016/j.brs.2014.12.004.
48. Ambrus GG, Antal A, Paulus W. Comparing cutaneous perception induced by electrical stimulation using rectangular and round shaped electrodes. Clin Neurophysiol. 2011;122(4):803–7. doi:10.1016/j.clinph.2010.08.023.
49. Paulus W. Transcranial electrical stimulation (tES – tDCS; tRNS, tACS) methods. Neuropsychol Rehabil. 2011;21(5):602–17. doi:10.1080/09602011.2011.557292.