Editorial

Transcranial direct current stimulation (tDCS) as adjunctive treatment in tobacco use disorder: *state of the art and future prospects*

La estimulación transcraneal con corriente directa (tDCS) como tratamiento coadyuvante en el trastorno por consumo de tabaco: situación actual y perspectivas de futuro

Raúl Espert-Tortajada, Marta Rebull-Monje and Marien Gadea-Doménech

Departamento de Psicobiología, Facultat de Psicología, Universitat de València.
Unidad de Neuropsicología, Hospital Clínico Universitario de Valencia.

Received: 24/02/2021 · Accepted: 05/03/2021

Abstract

Smoking is one of the world's leading preventable causes of premature illness and death. Nicotine is the pharmacological basis of addiction, and its dependence triggers a series of psychobiological, behavioral and cognitive changes. There are several effective strategies to help you quit smoking, but the long-term success rate is very low. Therefore, it is important to explore and study new alternative techniques for the treatment of tobacco use disorder (TUD), which can offer a greater variety of therapeutic resources and improve their results in the clinical setting. Recent studies of transcranial direct current stimulation (tDCS), applied to the dorsolateral prefrontal cortex (DLPFc), have shown promising results in reducing craving and tobacco consumption. Its use is justified by its important role in the regulation of inhibitory and reward control mechanisms (dopaminergic circuits), which are found to be dysfunctional in patients with TUD. The findings suggest that tDCS applied to DLPFc may be an effective technique as adjunctive therapy to help quit smoking. However, more research is needed and therefore future proposals are outlined.

Key Words

Addiction; tobacco; craving; give up smoking; neuromodulation; tDCS.

Correspondence:
Raúl Espert
Email: raul.espert@uv.es

Resumen

El tabaquismo es una de las primeras causas mundiales prevenibles de enfermedades y muertes prematuras. La nicotina es la base farmacológica de la adicción, y su dependencia desencadena una serie de cambios psicobiológicos, conductuales y cognitivos. Existen varias estrategias efectivas para ayudar a dejar de fumar, pero el porcentaje de tasas de éxito a largo plazo es muy bajo. Por lo tanto, es importante explorar y estudiar nuevas técnicas alternativas para el tratamiento del trastorno por consumo de tabaco (TCT), que puedan ofrecer más variedad de recursos terapéuticos y mejorar sus resultados en el ámbito clínico. Estudios recientes de estimulación transcraneal con corriente directa (tDCS), aplicada sobre la corteza prefrontal dorsolateral (CPFDL), han mostrado resultados prometedores en la reducción del *craving* y el consumo de tabaco. Su uso se justifica por su papel importante en la regulación de los mecanismos de control inhibitorio y recompensa (circuitos dopaminérgicos), que se encuentran disfuncionales en pacientes con TCT. Los hallazgos sugieren que la tDCS aplicada sobre la CPFDL, puede ser una técnica efectiva como terapia coadyuvante paya ayudar a dejar de fumar. Sin embargo, se necesita más investigación y, por ello, se describen propuestas futuras.

Palabras Clave

Adicción; tabaco; craving; dejar de fumar; neuromodulación; tDCS.

Smoking is one of the world's leading preventable causes of premature disease and death, represents a global epidemic with more than seven million deaths each year, and is a public health problem (World Health Organization [WHO], 2017). Nicotine is the pharmacological basis of addiction and its dependence triggers a series of psychobiological, behavioral and cognitive changes. Tobacco Use Disorder (TUS), according to DSM-V, is a chronic disorder that occurs with relapses and is characterized by a compulsive search for tobacco, which results in a loss of control in limiting its consumption and in the appearance of a negative emotional state when smoking is stopped (American Psychiatric Association [APA], 2013; Koob and Volkow, 2016).

Quitting smoking after a period of chronic or intermittent use is very difficult. Nicotinic withdrawal syndrome represents a set of unpleasant symptoms (anxiety, irritability, frustration, anger, depressed mood, restlessness, difficulty for concentrating and / or insomnia) that appear when tobacco use is stopped and that can precipitate relapse. Abstinence is accompanied by cognitive, structural and functional alterations typical of addictive disorders, which can make it difficult to stop using. There are three motivational processes that maintain addictive behavior: withdrawal symptoms, craving (intense desire to consume) and negative affect. Therefore, and in order to offer effective treatments to help people who want to quit smoking, and to guarantee better long-term abstinence rates, interventions should focus on alleviating these symptoms. In this sense, craving is a very important target of intervention, since it is one of the most frequent causes of relapse. However, current therapies based on psychopharmacology and psychology (cognitive-behavioral therapy) show limitations to adequately control the intense desire to smoke.

Smoking cessation has many health and quality of life benefits. Currently, there are several strategies to help quit smoking that are combined according to the degree of dependency and motivation of each person: cognitive behavioral therapy, nicotine replacement treatments (gum, patches, nasal spray, oral inhaler or nicotine lozenges) and drug treatments such as Bupropion and Varenicline. These treatments have been shown to be efficient and effective for smoking cessation (evidence A), but unfortunately relapse is still a very common phenomenon. Most smokers who quit with the help of drugs and psychotherapy relapse within the mean period of one year (Szasz, Szentagotai & Hofmann, 2012). Furthermore, despite the fact that pharmacological treatments show promising effects in the treatment of nicotinic addiction, it is known that in many people they present unpleasant adverse effects (insomnia, digestive problems or headaches, among others). On the other hand, it can be said that their mechanism of action on receptors is nonspecific and, consequently, they cannot achieve a localized intervention to address the underlying altered brain processes that facilitate relapse. Therefore, it is important to explore and study new alternative techniques for the treatment of TUD that can offer a greater variety of therapeutic resources and improve its results, since the percentage of long-term success rates is very low in people who try to stop smoking (Chawla and Garrison, 2018).

Transcranial direct current stimulation (tDCS) is a non-invasive neuromodulation technique that, through electrodes placed on the scalp, applies a small electrical current (1-2 mA) to a specific area of the brain, thus modulating the action potential of the resting membrane of cortical neurons. It consists of two poles, the cathode, which causes a decrease in cortical excitation due to the hyperpolarization of neurons, which decreases their firing probability, and the anode, which results in an increase in cortical excitability because it favors depolarization below the threshold, which increases the probability that neurons will increase the firing rate (Zhang *et al.*, 2019). The place of application of the electrodes, the power, the time and the direction of the current are programmed according to the pathology to be treated and its neurophysiological substrate. Specifically, the location is determined according to the Jasper international 10/20 system for the application of extracranial electrodes.

For decades, the tDCS technique has been widely used in neuroscientific research and in the evaluation and treatment of various neurological and psychiatric disorders such as addictive disorders, major depression or Alzheimer's disease. This is a safe technique, since no relevant side effects have been reported so far. Those that have been described are rare and mild, such as a slight itch on the scalp, local heat below the electrode or a slight burning sensation. Rarely, small skin lesions or behavioral effects have been documented (Antal *et al.*, 2017; Matsomoto and Ugawa, 2017). In addition to being safe, tDCS shows more advantages: it is non-invasive, cheap, accessible and easy to apply by expert professionals. Therefore, due to its qualities and characteristics, tDCS is a technique with very promising potential that, in our opinion and given our experience, is worth exploring.

The objective of tDCS in the treatment of addictive disorders is to modulate cortical excitability and improve the activity of neural circuits associated with cognitive control and craving, in order to reduce the problems associated with addiction (Zhao *et al.*, 2017). In other words, the use of tDCS in the approach to addictive disorders is justified by its important role in regulating the inhibitory and reward control mechanisms (dopaminergic circuits), which are found to be dysfunctional in patients with TUD. To date, the majority of published studies on substance use disorders have chosen neuromodulation of the dorsolateral prefrontal cortex (PFDLc) as a strategy to minimize addictive symptoms of nicotine. The PFDLc is involved in TUD along with a complex brain network that includes the amygdala and the medial prefrontal cortex. CPFDL is an area of the brain linked to cognitive control and executive functions, making it a good therapeutic target to help people quit smoking. Indeed, this region has shown in previous studies a benefit in the cognitive control of executive functions such as inhibitory control, attention and cognitive inhibition. For example, Loughead *et al.* (2015) observed that the hypoactivity in the PFDLc related to the working memory predicted the relapse in 81%, beyond the clinical and performance measures.

The evidence supports the relevance of PFDLc in relapse to TUD. Functional neuroimaging studies in patients with TUD indicate that PFDLc is significantly dysfunctional compared to the control group, since they show less activation and dysfunctional connectivity in the executive control network, which translates into greater difficulty in stopping the urge smoking and postponing its reward (Goldstein & Volkow, 2012). PFDLc also mediates behaviors reactive to cues associated with tobacco use. In people with TUD, all these networks have been affected, which interferes in the decision-making process and is related to the assumption of risky behaviors (Engelmann *et al.*, 2012). There are Functional Magnetic Resonance (fMRI) studies, such as the one by Yang *et al.* (2017), who have shown generalized changes in connectivity after the application of tDCS, due to the fact that the PFDLC is widely connected, structurally and functionally, with other areas of the brain. Therefore, another alternative hypothesis is that tDCS alters the functional connectivity between PFDLc and other brain regions involved in addictive disorder, which would mean that tDCS not only has local effects, but also produces network changes related to the connectome human brain (Fox *et al.*, 2014).

Most of the published tDCS studies on CPFDL in people with TCT have shown promising results in reducing craving and tobacco use (Fregni et al, 2008; Boggio *et al.*, 2009; Fecteau *et al.*, 2014; Meng *et al.*, 2014; Falcone *et al.*, 2016). Specifically, Fecteau *et al.* (2014) found that only 5 sessions, with the anode placed on the right PFDLc and the cathode on the left PFDLc, reduced craving and the number of cigarettes smoked until at least four days after the last tDCS session. Given that PFDLc is associated with executive functions and the attribution of salience to stimuli, these authors hypothesized that one of the beneficial effects of tDCS on nicotinic dependence could be the improvement of the control of impulsive and risky behavior, which it would allow making more functional decisions related to smoking behavior, that is, that smokers would gain greater self-control. Along the same lines, our research team recently carried out a study (pending publication), in which we applied 10 repeated sessions of tDCS at 1.5 mA for 20 minutes on PFDLc in people with TUD (cathode F3 and anode F4). The results have shown a significant reduction in nicotine dependence, in the number of cigarettes smoked and in the levels of carbon monoxide (CO) in the exhaled air. Additionally, we have observed a significant improvement in motivation and perceived self-efficacy to quit smoking. In this sense, the interaction between the effects of tDCS and motivation could support the notion that the main effect of tDCS could be mediated by higher-order cognitive functioning (Vitor de Souza *et al.*, 2018).

A recent meta-analysis carried out by Chen *et al.* (2020) has evaluated the effect size of tDCS on craving in substance use and eating disorders. They included, out of a total of 32 studies, 25 investigations of tDCS and addictive disorders, of which 8 were specific to TCT. The results showed a significant mean effect size in favor of the benefits of tDCS over the placebo group, that is, they found a significant decrease in post-tDCS craving and an increase in quality of life compared to the control group. In the same vein, another recent systematic review and meta-analysis (Kang, Kim and Kim, 2019), studied the effects of tDCS on CPFDL in people with TCT. After analyzing 12 studies with a total sample of 392 people who wanted to quit smoking, they concluded that this technique can be a good strategy to reduce addiction symptoms to nicotine. The results of the meta-analysis showed significant beneficial changes in cue-induced craving and smoking rate in the tDCS group. Indeed, Lefaucheur *et al.*, (2017) state that brain neuromodulation therapy for substance use disorders using tDCS in the CPFDL (cathode on the left front and anode on the right side) has reached a level of evidence B, which means that it is probably effective.

In summary, the conclusions derived from previous studies support the following hypotheses as the main possible mechanisms for reducing craving: 1) the tDCS neuromodulation of PFDLc induces and regulates neuronal plasticity, which could favor greater cognitive control; 2) the stimulation of PFDLc produces an activation in the dopaminergic pathways of the reward systems that, in turn, regulate the membrane potential of the pyramidal cells that alter glutamate tone and that, simultaneously, correlate with the release of GABA that contributes to greater plasticity. In conclusion, the evidence indicates that tDCS improves TUD symptoms with a decrease in craving and tobacco use. Furthermore, the results suggest that the application of tDCS in PFDLc may be a good objective to reduce craving and tobacco consumption and increase motivation and self-efficacy to quit smoking. Therefore, tDCS could be a useful technique as an adjunct treatment in smoking cessation interventions. However, more studies investigating the interaction between the effects of nicotine and tDCS are needed to find the optimal treatment strategy.

Regarding future directions, it would be interesting for future research to take into account the following proposals in order to consolidate the potential positive effects of tDCS on TUD: 1) Increase the sample; 2) Stratify the protocols to improve the comparability of the results obtained in the investigations; 3) Study alternative neuromodulation protocols; 4) Include neuroimaging studies to identify the mechanism of action of tDCS, specifically to see which are the modulated neuronal substrates associated with the decrease in craving and tobacco consumption; 5) Include other quantitative measures to evaluate the efficacy of tDCS on addictive behavior; 6) Propose the simultaneous use of standardized tasks to know their effect on the activation of cognitive control circuits during neuromodulation; 7) Investigate which modulating variables influence the effect of tDCS on TUD intervention; 8) Conduct longitudinal study designs to study the effects of repeated or prolonged exposure of tDCS; 9) Include studies that combine tDCS with cognitive-behavioral treatment or drugs, as it could enhance the beneficial effects of tDCS; 10) Study the potential use of tDCS at home under the supervision of a specialist. Regarding this last point, a guide has recently been published for the supervision by researchers of this technique applied at home with patients, in order to increase adherence to treatment, increase the number of sessions or carry out experimental designs ABAB (Leigh *et al.*, 2020).

Systematic research with tDCS in the clinical setting began in a decisive way from 2010 (although the technique began to be used in 2000), so we only have a little more than 10 years of studies that demonstrate its efficacy and safety in the TUD. Given the previous experience with Transcranial Magnetic Stimulation (TMS) and the growing scientific evidence, we have no doubt that sooner or later the FDA (Food and Drug Administration), the European Medicines Agency (EMA) and, finally, the AEMPS (Agencia Española de Medicamentos y Productos Sanitarios) will end up approving and regulating the clinical use of this cheap, safe and easy-to-apply neuromodulation technique that promises to be an ideal adjuvant for current therapies approved for TUD. One of the challenges we are currently facing with this technique is to resolve the question of how long the effects of this technique last and how often a recall session would have to be administered. Meanwhile, dozens of researchers and laboratories around the world continue their efforts to demonstrate through evidence the utility of tDCS in TUD.

REFERENCES

Alghamdi, F.; Alhussien, A.; Alohali, M.; Alatawi, A.; Almusned, T.; Fecteau, S.; Syed, S. H. and Shahid, B. (2019). Effect of transcranial direct current stimulation on the number of smoked cigarettes in tobacco smokers. *PLOS ONE*, 14 (2): e0212312 https://doi.org/10.1371/journal.pone.0212312

Antal, A.; Alekseichuk, I.; Bikson, M.; Brockmöller, J.; Brunoni, A.R.; Chen, R. and Fregni, F. (2017). Low intensity transcranial electric stimulation: safety, ethical, legal regulatory and application guidelines. *Clinical Neurophysiology, 128*(9), 1774-1809. https://doi.org/10.1016/j.clinph.2017.06.001.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing.

Behzad Rigi, K.; Behrooz, D.; Masoud, N.; Nour Mohammad, B.; Abed, M. and Mousa Chakeri, H. (2020). Combination Therapy and Opioids: Effectiveness of Transcranial Direct-Current Stimulation (tDCS) and Emotion Regulation Training in Reducing Current Drug Craving. *Maedica,* 15(1), 53–60. https://doi.org/10.26574/maedica.2020.15.1.53

Boggio, P.S.; Liguori, P, Sultani, N, Rezende, L, Fecteau, S. and Fregni, F. (2009). Cumulative priming effects of cortical stimulation on smoking cue-induced craving.

Neuroscience Letters 463, 82–86. https://doi.org/10.1016/j.neulet.2009.07.041

Chawla, M. and Garrison, K.A. (2018). Neurobiological Considerations for Tobacco Use Disorder. *Current Behavioral Neuroscience Reports*, 5(4), 238-248. https://doi.org/10.1007/s40473-018-0168-3

Chen, J.; Qin, J.; He, Q. and Zou, Z. (2020). A Meta-Analysis of Transcranial Direct Current Stimulation on Substance and Food Craving: What Effect Do Modulators Have? *Frontiers in psychiatry*, *11*, 598. https://doi.org/10.3389/fpsyt.2020.00598

Engelmann, J. M.; Versace, F.; Robinson, J. D.; Minnix, J. A.; Lam, C. Y.; Cui, Y.; Brown, V. L. and Cinciripini, P. M. (2012). Neural substrates of smoking cue reactivity: a meta-analysis of fMRI studies. *NeuroImage*, 60(1), 252-262. https://doi.org/10.1016/j.neuroimage.2011.12.024

Falcone, M.; Bernardo, L.; Ashare, R.L.; Hamilton, R.; Faseyitan, O.; Loughead, J. and Lerman, C. (2016) Transcranial Direct Current Brain Stimulation Increases Ability to Resist Smoking. *Brain Stimulation Journal 9*, 191–196. https://doi.org/10.1016/j.brs.2015.10.004

Fecteau, S.; Agosta, S.; Home-Blanchet, A.; Fregni, F.; Boggio, P.; Ciraulo, D. and Pascual-Leone, A. (2014). Modulation of smoking and decision-making behaviors with transcranial direct current stimulation in tobacco smokers: a preliminary study. *Drug and Alcohol Dependence 140,* 78–84. https://doi.org/10.1016/j.drugalcdep.2014.03.036

Fox, M.D.; Buckner, R.L.; Liu, H.S.; Chakravarty, M.M.; Lozano, A.M. and Pascual-Leone, A. (2014). Resting-state networks link invasive and noninvasive brain stimulation across diverse psychiatric and neurological diseases. *Proceedings of the National Academy of Sciences of the United States of America, 111*(41), E4367–75. https://doi.org/10.1073/pnas.1405003111

Fregni, F.; Liguouri, P, Facteau, S.; Nitche, M.A.; Pascual-Leone, A. and Boggio, P.S. (2008). Cortical stimulation of the prefrontal cortex with transcranial direct current stimulation reduces cue-provoked smoking craving: a randomized, sham-controlled study. *Journal of Clinical Psychiatry* 69, 32–40. https://doi.org/10.4088/jcp.v69n0105

Goldstein, R.Z. and Volkow, N.D. (2012). Dysfunction of the prefrontal cortex in addiction: Neuroimaging findings and clinical implications. *Nature Reviews Neuroscience 12*(11): 652-669. https://doi.org/10.1038/nrn3119

Kang, N.; Kim, R. K. and Kim, H. J. (2019). Effects of transcranial direct current stimulation on symptoms of nicotine dependence: A systematic review and meta-analysis. *Addictive behaviors,* 96, 133-139. https://doi.org/10.1016/j.addbeh.2019.05.006

Koob, G.F. and Volkow, N.D. (2016). Neurobiology of addiction : a neurocircuitry analysis. *The Lancet Psychiatry*, *3*(8), 760-773. https://doi.org/10.1016/S2215-0366(16)00104-8

Lefaucheur, J.P.; Antal, A.; Ayache, S.S.; Benninger, D.H.; Brunelin, J.; Cogiamanian, F.; Cotelli, M.; De Ridder, D.; Ferrucci, Langguth, B.; Marangolo, P.; Mylius, V.; Nitche, M.A.; Padberg, F.; Palm, U.; Pulet, E.; Priori, A.; Rossi, S.; Schecklmann, M.; … Paulus, W. (2017). Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). *Clinical Neurophysiology 128*: 56–92. https://doi.org/10.1016/j.clinph.2016.10.087

Leigh, E.; Charvet, M. T.; Marom Bikson, S.; Woods, A.J. and Knotkova, H. (2020). Supervised transcranial direct current stimulation (tDCS) at home: A guide for clinical research and practice. *Brain Stimulation 13* (3) : 686-693. https://doi.org/10.1016/j.brs.2020.02.011

Loughead, J.; Wileyto, E. P.; Ruparel, K.; Falcone, M.; Hopson, R.; Gur, R. and Lerman, C. (2015). Working memory-related neural activity predicts future smoking relapse. *Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology*, *40*(6), 1311–1320. https://doi.org/10.1038/npp.2014.318

Matsumoto, H. and Ugawa, Y. (2017). Adverse events of tDCS and tACS: a review. *Clinical Neurophysiology Practice, 2*, 19-25. https://doi.org/10.1016/j.cnp.2016.12.003

Meng, Z.; Liu, C.; Yu, C. and Ma, Y. (2014). Transcranial direct current stimulation of the frontal-parietal-temporal area attenuates smoking behavior. *Journal of Psychiatry Research* 54, 19–25. https://doi.org/10.1016/j.jpsychires.2014.03.007

Organización Mundial de la Salud (2017). WHO report on the global tobacco epidemic, 2017: Monitoring tobacco use and prevention policies. Geneva, Switzerland.

Szasz, P.L.; Szentagotai, A. and Hofmann, S.G. (2012). Effects of emotion regulation strategies on smoking craving, attentional bias, and task persistence. *Behaviour Research and Therapy*, 50(5), 333–40. https://doi.org/10.1016/j.brat.2012.02.010

Vitor De Souza Brangioni, M.C.; Pereira, D.A.; Thibaut, A.; Fregni, F.; Brasil-Neto, J.P.; Boechat-Barros, R. (2018) Effects of Prefrontal Transcranial Direct Current Stimulation and Motivation to Quit in Tobacco Smokers: A Randomized, Sham Controlled, DoubleBlind Trial. Frontiers in Pharmacology 9:14. https://doi.org/10.3389/fphar.2018.00014

Yang, L. Z.; Shi, B.; Li, H.; Zhang, W.; Liu, Y.; Wang, H. and Hudak, J. (2017). Electrical stimulation reduces smokers' craving by modulating the coupling between dorsal lateral prefrontal cortex and parahippocampal gyrus. *Social cognitive and affective neuroscience*, *12*(8), 1296-1302. https://doi.org/10.1093/scan/nsx055

Zhang, Y. ; Song, H. ; Chen, Y.; Zuo, L.; Xia, X and Zhang, X. (2019). Thinking on Transcranial Direct Current Stimulation (tDCS) in Reading Interventions: Recommendations for Future Research Directions. *Frontiers in Human Neuroscience*, 13:157. https://doi.org/10.3389/fnhum.2019.00157

Zhao, H.; Qiao, L.; Fan, D.; Zhang, S.; Turel, O.; Li, Y.; Li, J.; Xue, G.; Chen, A. and He, Q. (2017). Modulation of Brain Activity with Noninvasive Transcranial Direct Current Stimulation (tDCS): Clinical Applications and Safety Concerns. *Frontiers in Psychology 8:685*. https://doi.org/10.3389/fpsyg.2017.00685