EBioMedicine 57 (2020) 102839

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.elsevier.com/locate/ebiom

Commentary

Transcranial magnetic stimulation and addiction: Toward uncovering known unknowns

Vaughn R. Steele

Yale University, School of Medicine, Department of Psychiatry, 200 Retreat Avenue, Whitehall Building, Hartford, CT 06106, United States

ARTICLE INFO

Article History:
Received 1 June 2020
Accepted 1 June 2020
Available online xxx

Opioid use disorder (OUD), is a chronic, relapsing neurobiological brain disease of malleable circuits that became dysregulated with repeated drug exposure [1–3]. Establishing effective treatments for OUD is desperately needed to curb the opioid overdose crisis currently gripping the nation. New interventions must be tested for efficacy to modulate dysregulated circuits as a potential adjuvant to current OUD treatments. A promising tool garnering significant attention to target and treat dysregulated circuits is transcranial magnetic stimulation (TMS) [4].

By applying alternating magnetic pulses to the scalp, TMS induces neuronal firing in the targeted cortex and, potentially, its downstream connections. With a patterned, repetitive sequence of TMS, changes in the baseline electrical steady state may be achieved causing behavioral change. To establish TMS as a tool to modulate behavior, ostensibly due to long-term changes in circuitry after chronic TMS, Liu et al., [5] assessed craving scores before and after a TMS intervention. Drug craving elicits large-scale network activation [1–3] that is targetable with TMS applied to the scalp. Also, self-report craving, although subjective, is consistent within participant and is one of the primary outcome measures used to assess efficacy of OUD interventions.

A large sample ($N = 118$) of heroin users recruited from two treatment centers in China participated in the Liu et al., [5] study, recently published in *EBioMedicine*. Participants were split into three groups, two received a course of repetitive TMS (rTMS) and one served as a wait-list control. The TMS groups each received 20 daily sessions of rTMS at one of two frequencies (1 Hz vs 10 Hz). Craving scores were assessed before treatment and post-treatment (30, 60 & 90 days). All three groups reported a significant reduction in craving scores that persisted 60 days with the greatest reduction present in the TMS groups. Interestingly, there was no difference in craving scores between the two TMS groups.

There are two main contributions made by Liu et al., [5] in their recent work. First, based on the accepted historical perspective in the field, rTMS applied at 1 Hz should be inhibitory and 10 Hz should be excitatory [6] which would presumably lead to opposite behavioral outcomes. However, both TMS groups reported similar reductions in craving suggesting rTMS, regardless of frequency, is effective in reducing craving in participants with OUD. Second, the wait-list control group reported a reduction in craving without a TMS intervention. As was recently reported in a large placebo-controlled TMS intervention for depression [7], some individuals received benefit from being in the study without receiving the true intervention. Understanding placebo effects in rTMS interventions will go a long way to enhancing our effectiveness to treat addictions.

Much is yet unknown about implementing rTMS as an effective treatment for OUD, or any addiction for that matter. Certain known unknowns should be rigorously explored to uncover the most effective parameters to implement within individual reaping the greatest treatment rewards. Craving data from Liu et al., [5], although requiring replication, suggests frequency does not matter in reducing craving scores. Of course, many factors should be considered when interpreted results from any study; nonetheless, these findings are intriguing and worth further attention. What is not known in relation to these craving scores is whether the neural circuitry known to be dysregulated in OUD were modulated and thus the change in score was a manifestation of neuroplastic change induced by chronic rTMS. Neuroplastic change for dysregulated circuits holds tremendous potential and may be necessary to treat this biological brain disease [3].

As a field, we should work together on several fronts to thoroughly assess rTMS as an effective treatment for OUD. A recent consensus paper [8] outlines several parameters to consider as researchers work toward a common goal. Of primary interest highlighted here is to uncover induced neuroplastic change by rTMS applications. Our historical understanding that 1 Hz is inhibitory and 10 Hz is excitatory [6], and more recently continuous theta-burst stimulation (cTBS) is inhibitory and intermittent theta-burst stimulation (iTBS) is excitatory [9], was derived from stimulation of motor cortex. Most rTMS sessions applied as a treatment for clinical diagnoses target cortex beyond the motor cortex. Therefore, it is necessary to collect new measures of neuroplasticity at common rTMS targets (e.g., medial prefrontal cortex and left-dorsolateral prefrontal cortex). Simply recording neural measures (functional magnetic resonance imaging or electroencephalography) both before and after an rTMS session is essential to assess neuroplasticity by comparing pre/post measurements. This could be achieved at the group-level; however, we know there will be individual differences. Moving toward individualizing treatment for each patient will likely be the

DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2020.102809.
E-mail address: vaughn.steele@yale.edu

https://doi.org/10.1016/j.ebiom.2020.102839

most effective path forward. Using direct measures of dysregulated circuits is a direction the field should be moving [c.f. 10]. Although individualizing treatments is likely years, if not a decade, away, measuring induced neuroplasticity is within reach. In true scientific fashion, Liu et al., [5], take us one step closer to understanding rTMS as a treatment for OUD while uncovering new questions yet to be answered.

Author contribution

VRS wrote and finalized the manuscript.

Declaration of Competing Interest

Dr. Steele has nothing to disclose.

Acknowledgment

VRS is partially funded by the National Institute on Drug Abuse (NIDA) grant K12 DA000167 (Multiple PI: Potenza & O'Malley).

References

[1] Volkow ND, Koob GF, McLellan AT. Neurobiologic advances from the brain disease model of addiction. New Engl J Med 2016;374:363–71. https://doi.org/10.1056/NEJMra1511480.

[2] Steele VR, Pariyadath V, Goldstein RZ, Stein EA. Reward circuitry and drug addiction. In: Charney DS, Nestler EJ, Buxbaum J, Sklar P, editors. Neurobiology of mental illness. 5th Edition Oxford, UK: Oxford University Press; 2017.

[3] Steele VR, Ding X, Ross TJ. Addiction: informing drug abuse interventions with brain networks. Connectomics: applications to neuroimaging. Academic Press; 2019. p. 101–22.

[4] Diana M, Raij T, Melis M, Nummenmaa A, Leggio L, Bonci A. Rehabilitating the addicted brain with transcranial magnetic stimulation. Nat Rev Neurosci 2017;18:685–93. https://doi.org/10.1038/nrn.2017.113.

[5] Liu X, Zhao X, Liu T, Liu Q, Tang L, Zhang H, et al. The effects of repetitive transcranial magnetic stimulation on cue-induced craving in male patients with heroin use disorder. EBioMedicine 2020 In press.

[6] Pascual-Leone A, Tormos JM, Keenan J, Tarazona F, Cañete C, Catalá MD. Study and modulation of human cortical excitability with transcranial magnetic stimulation. J Clin Neurophysiol 1998;15:333–43.

[7] Yesavage JA, Fairchild JK, Mi Z, Biswas K, Davis-Karim A, Phibbs CS, et al. Effect of repetitive transcranial magnetic stimulation on treatment-resistant major depression in us veterans: a randomized clinical trial. JAMA Psychiatry 2018;75:884–93. https://doi.org/10.1001/jamapsychiatry.2018.1483.

[8] Ekhtiari H, Tavakoli H, Addolorato G, Baeken C, Bonci A, Campanella S, et al. Transcranial electrical and magnetic stimulation (tES and TMS) for addiction medicine: a consensus paper on the present state of the science and the road ahead. Neurosci Biobehav Rev 2019;104:118–40. https://doi.org/10.1016/j.neubiorev.2019.06.007.

[9] Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. Neuron 2005;45:201–6. https://doi.org/10.1016/j.neuron.2004.12.033.

[10] Drysdale AT, Grosenick L, Downar J, Dunlop K, Mansouri F, Meng Y, et al. Resting-state connectivity biomarkers define neurophysiological subtypes of depression. Nat Med 2017;23:28–38. https://doi.org/10.1038/nm.4246.