Transcranial alternating current stimulation for the treatment of obsessive-compulsive disorder?

Flavio Frohlich[*],

Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; Carolina Center for Neurostimulation, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; Department of Neurology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; Department of Cell Biology and Physiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; Department of Biomedical Engineering, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; Neuroscience Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Justin Riddle,

Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; Carolina Center for Neurostimulation, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Jonathan S. Abramowitz

Department of Psychology and Neuroscience, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Dear editor,

We read with great interest the recent report by Reinhart and colleagues on their transcranial alternating current stimulation (tACS) study that targeted orbitofrontal cortex for the modulation of reward-learning and obsessive-compulsive behaviors [1]. In a series of two elegant studies, linked by a computational model of reward-learning, the authors first show a selective impairment in optimal behavioral choices in a monetary reinforcement learning task in which participants learn the unequal rewards associated with different stimuli and accordingly adjust their choice behavior. This effect was only found for individualized beta-gamma tACS but not for alpha- or sham-tACS, suggesting that the effect of stimulation is frequency-specific and not a general electric effect. Furthermore, the authors report specificity with regards to task condition, as only the reward and not the punishment trials showed impairment by beta-gamma tACS. In the second experiment, a doubleblind, active-sham-controlled study of beta-gamma versus alpha-tACS was performed with "non-clinical" participants who exhibited obsessive-compulsive behaviors as measured

[*]Corresponding author. Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA. flavio_frohlich@med.unc.edu (F. Frohlich).

by OCI-R. The authors recruited participants with a wide-range of symptoms, which enabled analysis of baseline beta-gamma activity during reward-learning as a function of OCD symptom severity. Building on an emerging literature of tACS clinical trials in psychiatry [2-4], a five-day paradigm was used with follow-up visits up to 3 months. Beta-gamma tACS outperformed alpha-tACS in terms of symptom improvements, leading the authors to propose that such an intervention could be investigated in future clinical trials for the treatment of OCD.

This study raises several interesting questions that are important to be considered for this nascent field of non-invasive brain stimulation for the treatment of psychiatric disorders. First, the authors use a cutting-edge strategy of identifying their individually targeted neural oscillations by recording EEG during the task, extracting individual peak frequency, and adjusting the stimulation frequency [5,6]. Such frequency-matching is particularly important in the context of tACS where the mechanism of action (described in dynamical systems terms as the so-called Arnold tongue) requires frequency tuning for achieving entrainment of neural oscillations [7,8]. Second, any such mechanistic study requires demonstration of successful target engagement, in other words an answer to the question whether the stimulation had the desired effect (in this case presumably enhancement) on the targeted oscillation [9]. Evidence of the desired effect is critical given the recent debate about the efficacy of tACS in entraining and modulating neuronal oscillations [10-12]. There is no literature that would provide confidence in the proposed, simple one-to-one mapping of that a beta-gamma frequency waveform (selectively) enhances beta-gamma frequency endogenous oscillations across both healthy participants and participants with obsessive-compulsive behavior. Rather, the perturbation provided by tACS is sufficiently weak that the effects of stimulation depend on numerous features of the endogenous network activity at the time of stimulation [13]. Furthermore, as alluded by the authors, targeting interconnected networks with tACS can have counterintuitive effects on synchronization [14]. The lack of EEG evidence for successful target engagement in both experiments reported in this paper is a serious limitation that may be at the origin of the ultimately puzzling findings that the presumed enhancement of the reward-learning signal actually impaired learning behavior. In that vein, we do not recommend the use of vocabulary that incorrectly implies successful target engagement in absence of any evidence ("modulation of rhythms") since for all we know the effect of the stimulation of neural activity could be a counterintuitive decrease in beta-gamma activity. For example, a double-blind placebo-controlled clinical trial of tACS showed a decrease instead of an increase in alpha oscillations in response to alpha-tACS in patients with major depressive disorder [2]. Third, the authors frame their discussion of the neurophysiology around the orbitofrontal cortex, but the premise that the observed beta-gamma activity arises from the orbitofrontal cortex is speculative: motivated by a literature review rather than direct measurement. Thus, when the authors find increased amplitude of beta-gamma oscillations for reward trials at baseline, the activity is recorded from the frontocentral midline (as depicted in Fig. 1 of Grover et al., 2021). Source localization should be performed to assert that this activity arises from the orbitofrontal cortex as midline activity can also arise from homologous dipoles [15,16]. Furthermore, the stimulation montage was designed to target the orbitofrontal cortex. When we attempted to recreate the electric field distribution reported in the paper (using ROAST [17]), we found

that the stimulation has substantial off-target effects in lateral prefrontal cortex, primary motor and somatosensory cortex, and posterior cingulate cortex that may also explain the reported findings (Fig. 1).

From a clinical perspective, the results also open up some interesting questions that deserve further attention. The authors propose that modulating reward-learning could be a potential treatment strategy for obsessive-compulsive behaviors. It is indeed interesting to read that higher symptom scores were associated with better performance on the task, and that better performance was associated with decreased beta-gamma amplitude for reward trials. Additionally, participants with higher symptom scores showed a reduction in beta-gamma activity during reward trials. Thus, beta-gamma tACS presumably increased beta-gamma activity resulting in an impairment to reward-learning that decreased OCD symptoms. The fundamental relationships here are counterintuitive and intriguing. Typically, a stimulation paradigm will attempt to enhance a deficient rhythm that is associated with improved behavioral performance [18]; however, in this experiment, beta-gamma activity is maladaptive and a task is used in which a psychiatric illness ironically optimizes performance. Thus, disruption of performance is therapeutic. The associations presented in this experiment are logically consistent, yet do not lend insight into the neural mechanism of therapeutic action while still being an impressive demonstration of a novel treatment paradigm.

Practically, it remains unclear if the 5-day paradigm changed performance on the reward-learning task as this was not measured. If we assume that indeed reward-learning was impaired by the stimulation paradigm (as demonstrated by Experiment 1) then we wonder how such a paradigm can be of clinical efficacy. Obsessive-compulsive behaviors are rigid behaviors and compulsions are maintained as a maladaptive coping strategy for dealing with obsessive thoughts. Today, cognitive behavioral therapy (CBT) is the gold-standard, evidence-based treatment for OCD. Successful treatment heavily relies on learning alternative cognitive and behavioral responses to undesired thoughts. Thus, the open question remains how habits can be unlearned and less maladaptive behaviors can be learned if that very mechanism of reward-learning is impaired by the tACS paradigm as suggested by Experiment 1. Successful treatment of OCD requires extinction of habits which requires the development of behavioral flexibility, typically assessed by tasks that include a change in contingency. Of note, the task used by the authors does not probe behavioral flexibility but rather the ability to detect and appropriately "exploit" reward contingencies. This point is of interest since a recent rat study of substance use disorder showed restoration of behavioral flexibility with gamma-tACS, perhaps in contradiction to the reduced learning found here [19]. This further supports the notion that the behavioral effect of tACS (reduced learning) should be counter-productive towards a clinical improvement. The authors' argument that reward-learning leads to habit formation is well taken but it appears that in this framework beta-gamma tACS to OFC would rather serve to prevent the formation of obsessive-compulsive behaviors than to alleviate them as found in Experiment 2. Yet, it seems that gamma-tACS has potential for the treatment of OCD (albeit with a different spatial target) as reported in a case series of severe OCD cases that displayed remarkable symptom improvements [20]. It would have been interesting to learn the authors' thoughts on this study as part of their discussion. Especially since these findings contrast with the

findings reported by Reinhart and colleagues, which are clinically not noticeable due to their small size. The largest (yet still small) effects reported were for ordering (not specific to OCD) and for hoarding (not an OCD symptom). Together, it appears appropriate to strike a more cautionary tone about the therapeutic promise of the investigated tACS paradigm. Although we applaud the authors' efforts and we share their conviction that tACS holds great promise as a future therapeutic, overselling initial studies with limits of the kind discussed here will hurt instead of advance the field.

In conclusion, the study by Reinhart and colleagues demonstrates the promise of tACS in clinical applications but also demonstrates the importance of concurrent target engagement measures such as EEG, MEG or fMRI to ensure that there is indeed the proposed effect on neural activity. Only by decoding the mechanism of action will we be able to apply rational design to turn initial observations into clinical meaningful treatment paradigms.

Acknowledgements

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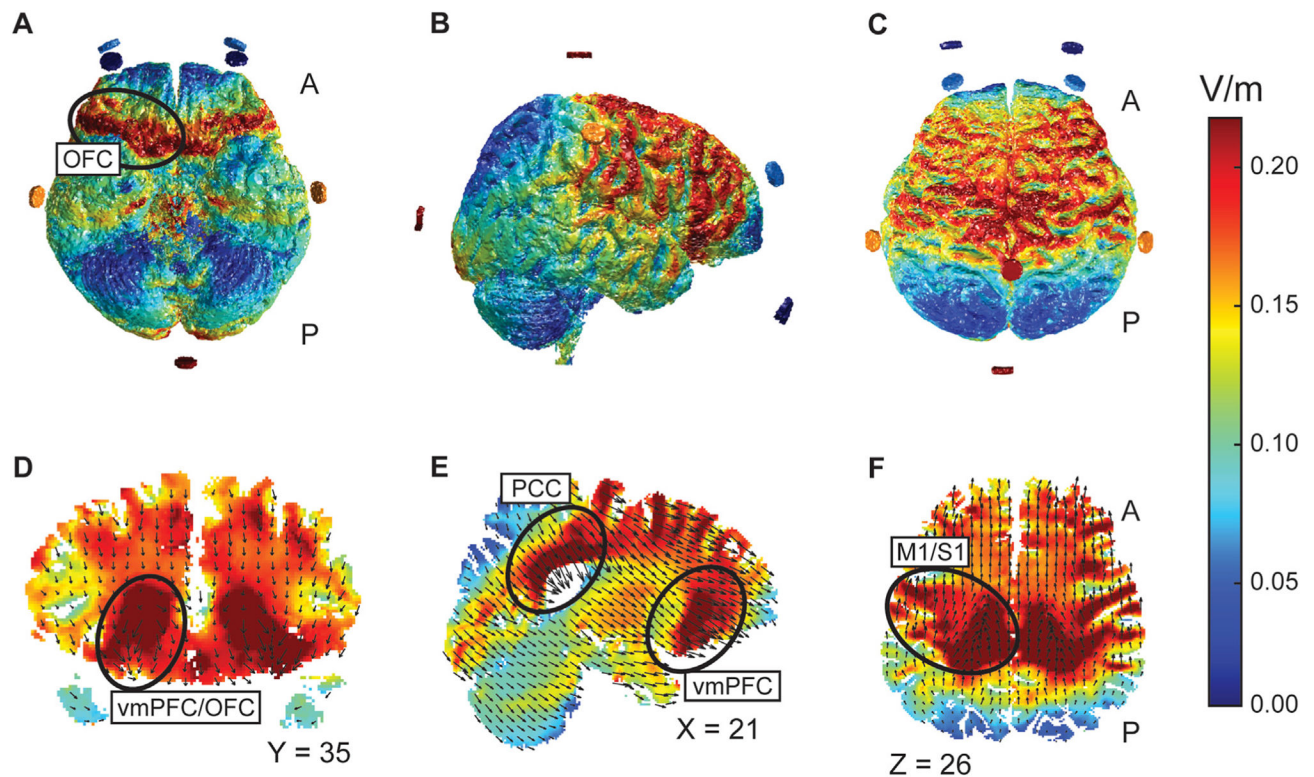
Fig. 1.
Electric field modeling for the montage used in Grover et al. *Nature Medicine 2021.* (A–C) Normalized electric field on the surface of the brain. (A) The axial-ventral view replicated the e-field model displayed in Fig. 1 of Grover et al., 2021 with peak activation in the orbitofrontal cortex (OFC). (B) The lateral view displayed peak electric field in lateral frontal cortex. (C) The axial-dorsal view showed peak electric field at the medial central sulcus. (D–F) Normalized electric field and electric field vectors in cross-sectional slices selected to depict maximal electric field strength. (D) Coronal slice at MNI coordinate (Y = 35) with electric field vectors in anterior prefrontal cortex (PFC). Peak electric field in ventromedial PFC (vmPFC) and OFC. (E) Sagittal cross-section (X = 21) replicates the e-field model depiction in Grover et al., 2021. E-field peaks were found in posterior cingulate cortex (PCC) and vmPFC. (F) Axial cross-section (Z = 26) depicts peak electric field strength near the central sulcus encompassing primary motor cortex (M1) and primary somatosensory cortex (S1). Units are volts per meter (V/m).