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LETTER TO THE EDITOR

Transcranial alternating current stimulation (tACS) as a treatment for fibromyalgia syndrome?

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Dear Editor:

We have read with great interest the recent report on a pilot clinical trial of transcranial alternating current stimulation (tACS) for the treatment of fibromyalgia syndrome (FMS) [1]. In this pilot study, 11 patients with FMS received 10 days of tACS combined and 10 days of transcranial random noise stimulation (tRNS), both combined with physical therapy, in a randomized, double-blind cross-over study. Fifteen patients completed one arm of the study. The authors individualized stimulation by comparing the topology of spectral amplitude in 5 canonical bands (delta, theta, alpha1, alpha2, and beta) from resting-state EEG with healthy controls; 11 of 15 participants received stimulation at 30 Hz, whereas the remaining 4 participants received stimulation at 4 Hz for the tACS condition. While the idea for this trial is certainly exciting, we are concerned about several pronounced shortcomings of the presented results that we feel have not received sufficient attention in the published manuscript.

First, the reported clinical improvement is puzzling and does not seem to support a clinical efficacy of the employed protocol. We had to consult the supplementary materials to find the numbers reported for the preregistered symptom outcomes of the study, Visual Analog Scale for pain (VAS) and Short-Form 36-Item Health Survey (SF-36). It seems that there was no second baseline assessment after crossing over participants, which is highly concerning. Also, it seems that for the reported median values, the effect of tACS and tRNS on VAS were exactly the same (first row of table T6) and the impact on SF-36 was nearly identical (final row of table T2). Not reporting these null findings for the primary outcomes in the main paper is a highly questionable practice. Rather, the report seems to be based on the fact that nine responded to tACS and seven responded to tRNS, hardly an impressive difference that does not seem to have been tested with an appropriate statistical method. Detailed and precise reporting of findings is key for reproducible science and for advancing the field.

Second, we are concerned about the lack of details and the choice of methods for non-invasive brain stimulation. It seems that the stimulation paradigm employed may not actually be tACS since it appears that the amplitude was modulated between 1 and 2 mA, which seems to suggest that there was a DC offset included in the stimulation, which is not justified and may severely impact the interpretation of the results. Overall, the methods as reported are unclear as to the stimulation waveform for tACS. We are also surprised by the choice of tRNS as a control condition since tRNS may have a similar effect to tACS by means of stochastic resonance [2] and an active-placebo control condition or a control frequency would have provided more convincing evidence for successful target engagement by tACS. Furthermore, at least one previous study has found that the application of tRNS was effective at reducing self-reported pain for patients with multiple sclerosis [3].

Third, no evidence is presented if the study blind was successfully maintained. The authors made an unusual choice of a spectrum from 0 to 100 Hz for tRNS when tRNS has been shown to be more effective when applied at higher-frequencies > 100 Hz [4]. Similar to tACS, the stimulation may

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have included a DC offset if the amplitude of applied current was only modulated from 1 to 2 mA. Given that tRNS has known effects on cortical excitability, it would be important to know what side-effects the participants experienced and if either participants or study personnel were able to guess the stimulation condition above chance probability. This is a vital piece of information for any double-blind study.

Fourth, the study does not conceptually distinguish between a shift in frequency and a change in power of a given oscillation. For example, FMS is associated with a pathological slowing of the alpha oscillation within the range of 8–12 Hz [5], not cited by the authors, as well as an increase in the amplitude of frontal-midline theta oscillations [6], cited by the authors. Capturing a shift in alpha frequency by comparing power between canonical frequency bands (alpha1 and alpha2) is at best an indirect measure of the underlying neurophysiological phenomenon and at worst a wrong conceptualization leading to wrong conclusions. Alternatively, if the goal was to suppress the amplitude of theta oscillations, then it would be inappropriate to deliver stimulation in theta-frequency based on the presented logic of the stimulation parameter selection. Thus, the presented stimulation framework is a sort of "re-balancing" of the power spectra. This framework more accurately parallels an emerging literature that has found that the aperiodic signal (relative power between high and low frequencies) may reflect the excitatory-inhibitory balance of the brain [7]. Thus, the decision to deliver stimulation at a low frequency (4 Hz) or a high frequency (30 Hz) might be conceptualized as a method to shift the aperiodic slope of the spectrum. However, there is no study to our knowledge that has associated alterations in the aperiodic signal with FMS or chronic pain.

Fifth, we were surprised to see that the authors did not connect their results to previous work on tACS for chronic pain from our group [8]. We have shown in a double-blind placebo-controlled trial that a single session of alpha-tACS administered to the sensory-motor cortical area significantly restored alpha oscillation power, which was correlated with symptom improvement in this population of patients with chronic low back pain. Importantly, we showed in the same study that symptom severity at baseline was negatively correlated with the power of the alpha oscillation. We feel that these results serve as a helpful template for the interpretation of the increased alpha oscillation power reported in the study.

In summary, we are highly enthusiastic about the application of tACS for FMS and applaud the intention of the authors. However, we are concerned that the study in its current published form has numerous fundamental caveats that seem weaken the claims made by the authors and require attention for the field to move forward towards rigorous clinical trials of tACS.

Declarations

Conflict of interest FF is the lead inventor of IP filed by UNC. Flavio Frohlich is founder, shareholder, and chief science officer of Pulvinar Neuro, which did not play any role in the writing of this article. FF has received honoraria from the following entities in the last 12 months: Sage Therapeutics, Academic Press, Insel Spital, and Strategic Innovation. JR has no conflict of interest.

References

1. Bernardi L et al. (2020) Beyond physiotherapy and pharmacological treatment for fibromyalgia syndrome: tailored tACS as a new therapeutic tool. Eur Arch Psychiatry Clin Neurosci
2. Antal A, Herrmann CS (2016) Transcranial alternating current and random noise stimulation: possible mechanisms. Neural Plast 2016:12
3. Palm U et al (2016) Effects of transcranial random noise stimulation (tRNS) on affect, pain and attention in multiple sclerosis. Restor Neurol Neurosci 34(2):189–199
4. Terney D et al (2008) Increasing human brain excitability by transcranial high-frequency random noise stimulation. J Neurosci 28(52):14147–14155
5. Lim M et al. (2016) Increased low- and high-frequency oscillatory activity in the prefrontal cortex of fibromyalgia patients. Front Human Neurosci 10(111)
6. Fallon N et al (2018) Altered theta oscillations in resting EEG of fibromyalgia syndrome patients. Eur J Pain 22(1):49–57
7. Donoghue T et al (2020) Parameterizing neural power spectra into periodic and aperiodic components. Nat Neurosci 23(12):1655–1665
8. Ahn S et al. (2018) Identifying and engaging neuronal oscillations by transcranial alternating current stimulation in patients with chronic low back pain: a randomized, crossover, double-blind, sham-controlled pilot study. J Pain