CME Article

Transcranial Alternating Current Stimulation (tACS) for Major Depressive Disorder

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ABSTRACT

The 21st century has brought forth major advancements in device-based treatments for psychiatric disorders such as major depressive disorder (MDD). One of the most exciting technologies on the rise in this field is transcranial alternating current stimulation (tACS). The small but rapidly growing body of knowledge on tACS suggests that this wearable, low-cost, noninvasive neuromodulation method could provide a safe and effective alternative, or augmentation, to pharmacological interventions for MDD. While device parameters for treatment of MDD need refinement before this method is ready for standardized clinical use, we expect that tACS will make a significant impact on psychiatric treatment in the coming years. **[*Psychiatr Ann*. 2022;52(11):456-460.]**

Transcranial alternating current stimulation (tACS) is a wearable, noninvasive brain stimulation technique. This approach is relatively understudied compared to other transcranial stimulation methods, such as repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS); however, preliminary case studies and pilot trials show promising results that encourage further investigation. This technology has the potential to provide a low-cost, safe, and convenient alternative to standard treatments for major depressive disorder (MDD).

MECHANISM OF ACTION

tACS is a transcranial treatment method that stimulates the brain by passing a low-amplitude alternating current between electrodes placed on the

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scalp. The resulting sinusoidal electric field is similar to that of a naturally occurring brain oscillation.[1] By introducing a low-intensity current at the desired parameters, tACS compels endogenous oscillations to mimic the frequency and phase of the exogenous current.[2,3] This phenomenon is known as "entrainment." Previous studies have found that tACS can entrain, and augment, naturally occurring brain oscillations[4] and enhance cognitive performance[5-7] within neurotypical individuals. Studies in both humans and nonhuman primates confirmed that these effects were specific to the location and frequency at which tACS was applied.[2,8] Therefore, it is essential that the parameters of tACS are tailored to the condition that is being targeted with the treatment.[9] In recent years, investigators have focused on finding the parameters best suited to addressing specific neurological and psychiatric disorders, including MDD. Given its power to enhance both cognitive and electrophysiological performance, tACS has the potential to provide symptomatic relief to people with MDD.

APPLICATION IN MDD

Although there is no "biomarker for MDD," there is growing evidence for disorganized and altered network oscillation associated with MDD. One line of evidence suggests that frontal alpha oscillations (and their dynamic regulation in response to stimuli of high emotional salience and valence) are dysregulated in MDD.[8] Specifically, elevated alpha oscillations in the left frontal cortex have been shown to correlate with reduced approach motivation (ie, motivation arising from the desire for a positive stimulus).[10,11] rTMS over the left dorsolateral prefrontal cortex (dlPFC) can relieve symptoms of MDD.[12] Although the rTMS stimulation frequency was chosen due to technical constraints at the time, it has become clear that rTMS may be effective due to its action on alpha oscillations (8 to 12 Hz), potentially through a homeostatic rebalancing of left and right frontal alpha oscillations.[13-15] In a recent study, our team at the University of North Carolina (UNC) hypothesized that 10-Hz tACS would have a similarly therapeutic effect on symptoms of MDD. This double-blind pilot trial compared 10 Hz, 40 Hz, and sham tACS in adults with MDD. We hypothesized that 10-Hz tACS would be significantly more efficacious than the other two conditions. Thirty-two patients with MDD received tACS daily for 5 consecutive days. Stimulation electrodes were placed over the frontal lobe (International 10/20 placements F3 and F4), with a return electrode along the midline (International 10/20 placement Cz). The two frontal electrodes had a zero-to-peak amplitude of 1 mA and the return electrode had an amplitude of 2 mA. Participants who were randomly assigned to one of the two active tACS groups received 40 minutes of in-phase stimulation over the left and right dlPFC at either 10 Hz or 40 Hz. Participants in the sham group received 10-Hz tACS for 40 seconds.[16]

Our UNC team found that, although all three groups exhibited a decrease in depressive symptoms, participants in the 10-Hz group had a significantly higher response rate (77.8%) at 2 weeks after treatment compared to those in the 40-Hz and sham groups (30% and 20% response rates, respectively). Furthermore, electroencephalogram (EEG) analysis revealed that participants in the 10-Hz group exhibited reduced left frontal alpha activity on the final day of treatment compared to baseline.[16] The outcome of this study suggests that tACS can reduce depressive symptoms in adults with MDD. Furthermore, this study demonstrates that tACS can effectively modulate endogenous brain oscillations in adults with MDD. Importantly, a recent randomized clinical trial (RCT) successfully replicated the reduction in left frontal alpha oscillations by tACS (targeted to the individual peak alpha frequency) when compared to placebo-tACS. Stimulation selectively decreased the left frontal alpha oscillations elicited by visual stimuli that were rated as positive by the participants. Given the inhibitory role of alpha oscillations, this finding can be interpreted as an increase in engagement of left frontal cortex in response to positive stimuli.[17]

A few months after participating in the UNC pilot study, one patient from the 10-Hz group who responded to the initial course of treatment returned for another course of 10-Hz tACS. The participant received tACS treatment once a week for a period of 12 weeks. By the end of the treatment course, this participant had achieved remission from MDD, according to both self-reported and clinician-rated scales. Two months after treatment, the participant was still in remission,[18] providing further support for the efficacy of tACS.

This pilot trial conducted by our UNC team is the largest study on tACS in MDD published to date. However, there are several other case studies that provide additional support for the use of tACS in MDD. One case series explored the effect of 40-Hz tACS on mood and cognition in 6 patients with MDD. Half of the patients received tACS twice daily for 10 minutes, and the other half received tACS once daily for 20 minutes. All patients received bilateral in-phase stimulation over F3 and F4 with a zero-to-peak amplitude of 1 mA. The treatment course was 5 days a week over 2 weeks, for a total of 10 treatments. All 6 patients experienced reduced symptoms of MDD, and the patients who received twice-daily treatment experienced greater improvement.[19] An additional case study reported the results from a pregnant woman who received weekly 20-minute treatments of 40-Hz tACS for 9 weeks. This patient achieved remission that was sustained for at least 3 months after treatment.[20]

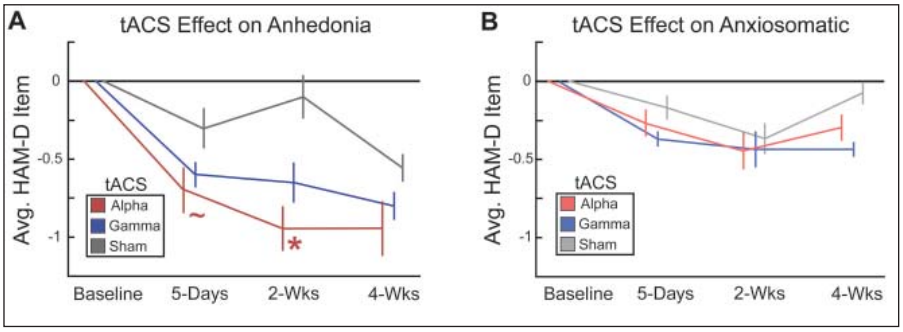

Figure 1. Analysis of the treatment effect from Alexander et al.[16] as a function of symptom subtype. Five days of transcranial alternating current stimulation (tACS) were delivered in alpha-frequency (10 Hz), gamma-frequency (40 Hz), and sham. Depressive symptoms were measured after treatment, at a 2-week follow-up visit, and at a 4-week follow-up visit. (A) The average reduction in HAM-D items for anhedonia ("work/activities" and "psychomotor retardation") was significantly greater with alpha-tACS than sham at the 2-week follow-up visit. (B) There were no statistically significant differences in anxiosomatic symptoms ("anxiety-somatic," "insomnia-early," "insomnia-middle") between active and sham stimulation. $^{*}P < .05$; $^{\sim}P < .1$. Error bars are within participant standard error of the mean.

DIMENSIONAL RESPONSE IN MDD

Recent research has suggested that there are distinct subtypes within the umbrella category of MDD. For example, a landmark study found that depressive symptoms, measured by the Hamilton Depression Rating Scale (HAM-D), could be clustered to predict different patterns of connectivity in functional MRI.[21] One dimension of MDD was identified as loading most heavily on HAM-D items related to anhedonia and the second was referred to as the anxiosomatic dimension. Additional datasets confirmed these symptom dimensions.[22,23] Based on the recent findings, our UNC team reanalyzed our clinical trial for MDD to better understand which specific symptoms were reduced by alpha-frequency tACS, which is reported here.

For our analysis, we adopted the HAM-D items chosen by Drysdale et al.[27] and averaged two clusters of symptoms, one related to the anhedonia dimension ("work/activities" and "psychomotor retardation") and the second related to anxiosomatic dimension ("anxiety-somatic," "insomnia-early," and "insomnia-middle"). Next, we investigated the change in these symptom dimensions from baseline for each tACS frequency: active stimulation with alpha-frequency (10 Hz), active stimulation with gamma-frequency (40 Hz), and sham/placebo. We found that there was a significant reduction in the average anhedonia HAM-D dimension with the 10-Hz tACS relative to sham-tACS at the 2-week follow-up visit ($t(17) = -2.382$, $P = .029$, $d = 1.093$) and a trend toward significance on day 5 after treatment completion ($t(18) = -1.852$, $P = .081$, $d = 0.854$) **(Figure 1A)**. There was no significant reduction in anhedonia symptoms following 40 Hz tACS (2-week follow-up: $t(18) = -1.656$, $P = .115$, $d = 0.741$). Furthermore, there was no reduction in the average HAM-D item for anxiosomatic symptoms at any time point for 10-Hz tACS versus sham-tACS (2-week follow-up: $t(17) = -0.278$, $P = .785$, $d = 0.128$) **(Figure 1B)**. Altogether, these findings suggest that the reduction in depressive symptoms with bilateral prefrontal 10-Hz tACS was driven by the reduction in symptoms of anhedonia. This selective effect is in agreement with the above-discussed role of frontal alpha oscillations in approach motivation. Furthermore, these findings emphasize the importance of considering the heterogenous symptom presentation of patients with MDD and suggest that noninvasive brain stimulation interventions, such as tACS, may reduce specific symptoms dependent on the frequency and site of stimulation.

TREATMENT PARAMETERS

The treatment parameters used in tACS studies for MDD vary widely, with treatment courses ranging from 5 days to 12 weeks, administrations ranging from daily to weekly, and treatment durations lasting from 10 minutes to 40 minutes. Researchers have consistently targeted the dlPFC in their efforts to address MDD with tACS, however, it is unclear whether a 10-Hz or 40-Hz frequency is more efficacious. Moreover, tACS may not be a "one size fits all treatment." Research has yet to delve into personal factors affecting the efficacy of tACS. A structured process of target identification, target engagement, and target validation will be invaluable for the further advancement of tACS.24 Overall, the most promising and feasible approach is likely the individualization of stimulation parameters based on EEG signals in the form of closed-loop stimulation.[25]

SAFETY AND TOLERABILITY

Studies of tACS in depression, as well as in neurotypical controls and in those with other neurological disorders, have consistently concluded that tACS is a safe treatment. Some minor side effects have been reported, including skin sensations, phosphenes (perception of flickering light caused by stimulation of the optic nerve), mild dizziness, headache, and lucid dreaming (when stimulated during sleep).[2,26,27] None of these side effects are known to persist long beyond the stimulation session and no serious adverse events have been reported in the use of tACS.[2,27,28] Providers and users should be advised that the safety and tolerability of tACS is under-studied compared to more established electrical stimulation methods, such as tDCS and rTMS. Therefore, it is not yet possible to rule out the possibility of new or longer

lasting side effects. However, given the well-known safety limits for electric current density, the discovery of novel side-effects is highly unlikely.[29]

AVAILABLE AND MARKETED DEVICES

There are several commercially available tACS devices, including the 1 × 1 transcranial Electrical Stimulation (1 × 1 tES) device by Soterix Medical, the XCSITE device from Pulvinar Neuro, and the neuroConn DC Stimulator Plus by Neurocare.[30] Four of the five studies of tACS in MDD detailed in this article employed neuroConn stimulators[16,18-20] and one employed the Pulvinar Neuro device;[17] however, these devices are currently only appropriate for research settings, because they have not been approved by the US Food and Drug Administration (FDA) for clinical use. Studies with these tACS devices have routinely received a nonsignificant risk designation by local institutional review boards. The UNC team has recently received confirmation for such status directly from the FDA for an ongoing tACS trial in MDD with the Pulvinar Neuro device.

CONCLUSIONS

Results of preliminary investigations of tACS in MDD are promising but are by no means definitive. More robust data sets and in-depth research are necessary before reliable conclusions can be made. We predict that the next few years will bring larger studies aimed at obtaining FDA approval of tACS for the treatment of MDD and other neuropsychiatric disorders.

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