Closed-Loop Transcranial Alternating Current Stimulation for the Treatment of Major Depressive Disorder: An Open-Label Pilot Study

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Major depressive disorder (MDD) is a leading cause of morbidity and disability with sharply increased prevalence through the COVID-19 pandemic, which was not matched with an increase in treatment options (1). This treatment gap highlights the urgent need for the development of novel treatment paradigms that are safe, effective, and accessible. Non-invasive stimulation has emerged as a promising network-based treatment approach for targeting the brain networks of depression symptoms with electromagnetic energy. Today's stimulation paradigms mostly focus on specific spatial networks and are not designed to target the temporal structure of large-scale brain activity, which typically exhibits rhythmic patterns referred to as network oscillations. These oscillations emerge from the synchronous activation of neuronal populations and are pathologically altered in depression and other psychiatric illnesses (2).

Pathological increase of alpha oscillations (8–12 Hz), specifically in the prefrontal cortex, represents a promising stimulation target due to its association with depression symptoms (3). For example, transcranial alternating current stimulation (tACS) for targeting frontal alpha oscillations (10 Hz-tACS) decreased the power of alpha oscillations and depression symptom severity in persons with MDD after a 5-day intervention in a double-blind randomized controlled trial (4). The mechanism of action of tACS is based on the synergistic interaction of endogenous oscillatory activity and the rhythmic weak electric fields applied by scalp electrodes (5). Thus, the response to stimulation depends on the state of the network, which leads to heterogenous stimulation outcomes in absence of individualized and dynamically adjusted stimulation paradigms (6). Accordingly, personalizing tACS to target the dynamical fluctuations of endogenous oscillations may improve clinical efficacy by more effectively engaging neural circuits through resonant properties (7, 8). Indeed, a follow-up investigation using tACS at individualized alpha frequencies (IAF) replicated a reduction in left frontal alpha power within a single session in people with MDD (9). While feedback tACS that responds to specific rhythmic activity features by adjusting the stimulation waveform in real-time was shown to augment sleep spindles and memory consolidation in healthy participants (10), this targeted approach has yet to be examined as a potential treatment for MDD.

Here we report on the first clinical trial of closed-loop tACS (CL-tACS) in MDD. Brief periods of tACS were triggered by fluctuations in IAF power measured via electroencephalography (EEG). This closed-loop approach enhances target engagement by leveraging the dynamical interaction between brain state and stimulation (11) and is thus hypothesized to improve clinical efficacy.

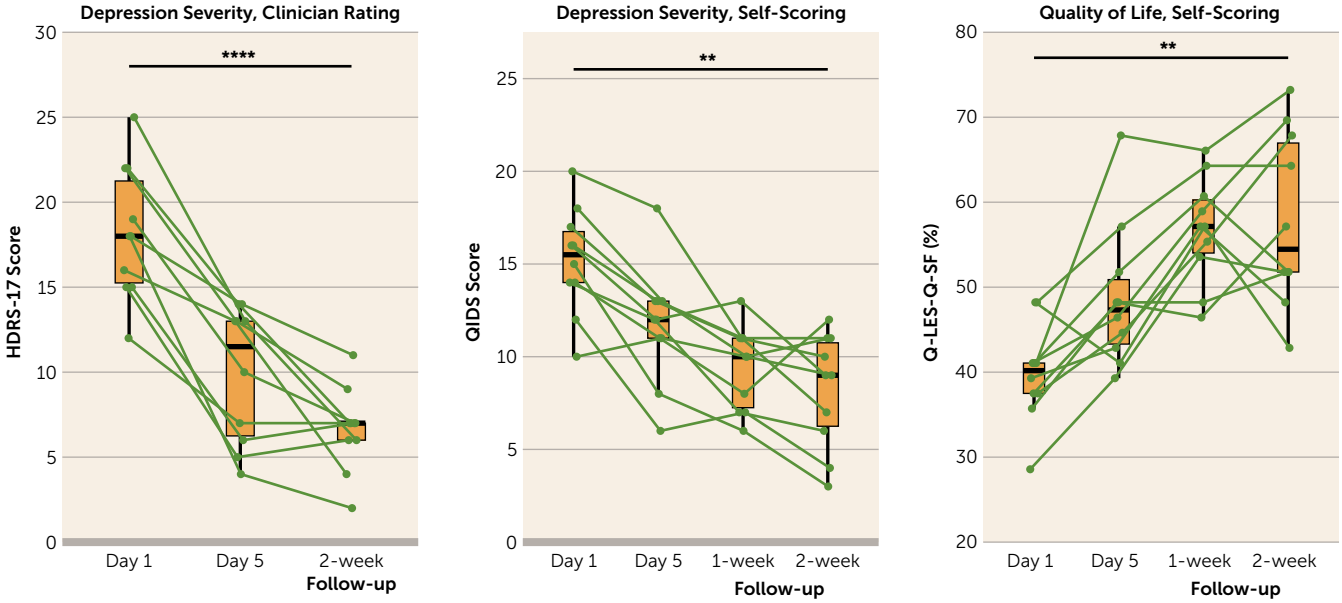
METHODS

This industry-sponsored, open-label clinical trial in patients with MDD applied CL-tACS for five consecutive days. MDD diagnosis was established by three experienced psychiatrists (D.R., Z.F., T.S.) and subsequently confirmed with the Mini-International Neuropsychiatric Interview (M.I.N.I.); participants were those with Hamilton Depression Rating Scale (HDRS-17) $>$ 8, stable antidepressant medication, and low suicide risk as determined with the C-SSRS-Triage. Exclusion criteria were standard contraindications for non-invasive brain stimulation studies (12), presence or history of severe alcohol use disorder, moderate to severe substance use disorder, bipolar disorder, psychotic disorder, schizophrenia, autism, current use of benzodiazepines $>$20 mg diazepam equivalent, and recent (3 months) history of rTMS, ECT, or (es)ketamine treatment. The study was registered at ClinicalTrials.gov (NCT05772702) and performed in the Carolina Center for Neurostimulation in the UNC Department of Psychiatry.

Study Procedure

After providing written informed consent, participants received bifrontal CL-tACS with zero-to-peak intensity of 2 mA. The stimulation montage matched previous reports of tACS for the treatment of MDD (4, 9). Single channel EEG was recorded with electrodes at Fz and Oz with a ground on right-mastoid. The stimulation frequency was tailored daily to the IAF identified during a 60-second, eyes closed resting state recording. Next, a 60-second, eyes open recording was collected, and the integrated power over IAF+/-2 Hz was

FIGURE 1. Depression severity and quality of life measures[a]



[a] Left: change in Hamilton Depression Rating Scale (HDRS-17); middle: change in Quick Inventory of Depressive Symptomatology (QIDS); right: change in Quality of Life Enjoyment and Satisfaction Questionnaire - Short Form (Q-LES-Q-SF). Depression symptoms were significantly reduced after CL-tACS both for clinician-rated and self-report depression scales. Quality of life significantly improved. Statistical significance is only marked for the Day 1–2-week follow-up post-hoc t test (pre-registered primary outcome). **** $p<0.001$, ** $p<0.01$.

used to set a triggering threshold for stimulation. During the session, stimulation was triggered when IAF power estimated from 10-second segments exceeded this threshold. Participants watched a neutral, relaxing video of underwater landscapes to standardize visual input. For all sessions, stimulation trains consisted of 120 seconds of tACS (20-second ramp up/down). The session was complete when either 15 stimulation trains occurred, or a maximum session duration of 60 minutes was reached.

Outcome Measures

Clinical assessments were performed on day 1 and day 5 prior to stimulation as well as on follow-up visits 1 week (self-report only) and 2 weeks after completion of the treatment. A stimulation-specific side effect questionnaire was administered after each stimulation session, and an adverse event questionnaire was administered on day 5 (both Likert Scale 0–3; absent, low, medium, severe). The primary outcome was change in HDRS-17 scores 2 weeks post treatment. Secondary outcomes included remission/response rates, self-report measures of depressive symptoms (QIDS, DASS-42), quality of life (Q-LES-Q-SF), and IAF power from daily pre-treatment, eyes open recordings.

Statistics

We employed a repeated-measures analysis of variance (RM-ANOVA), considering timepoint as within-subject factor with clinical scores and IAF power as dependent variables. The threshold for statistical significance was set at $\alpha=0.05$. Post hoc comparisons were conducted using two-tailed paired t tests. No correction for multiple comparison was applied. Exploratory Pearson correlations were conducted between HDRS-17 scores and IAF power percent changes at each day.

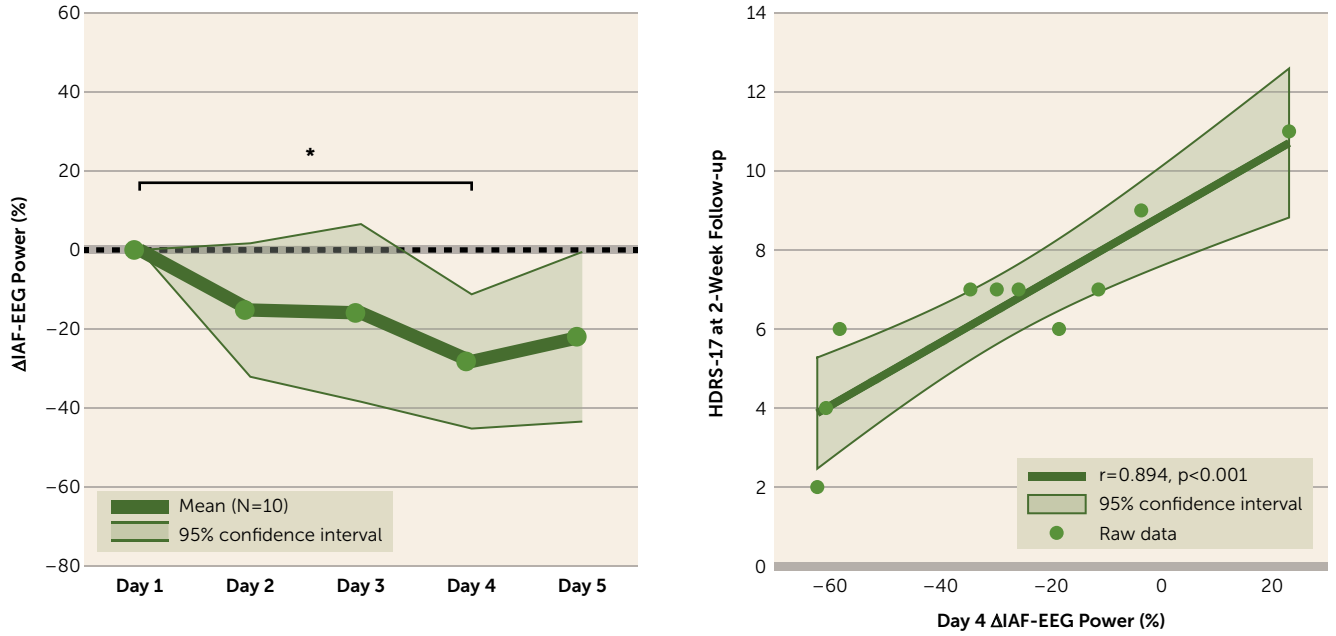
RESULTS

Eleven participants consented. Ten participants (8 females, 1 male, 1 gender nonconforming) with a mean age of 40.2 years (SD=13.4) and 11.4 months (SD=9.45) of current depressive episode completed at least four treatment sessions and were included in the analysis. All but two participants took antidepressant medication. Baseline depression severity was moderate on average (HDRS-17, M=18.2, SD=3.94) and treatment resistance assessed with the Maudsley Staging Method was mild (M=5.9, SD=1.2). One participant only completed four days of treatment, so a last observation carried forward approach was used for IAF power. No clinical data was interpolated. Only 3 of 49 sessions ended without triggering all 15 tACS trains, resulting in an average of 146 min (SD=9.24) total stimulation time across 5 days for each participant.

Clinical Results

CL-tACS significantly decreased depression severity over time assessed with both clinician-rated (HDRS-17, $F[2,18]=49.39$, $p<0.001$, $\eta^2=0.85$), and self-report measures (QIDS, $F[3,27]=20.99$, $p<0.001$, $\eta^2=0.7$; DASS-42 Depression, $F[3,27]=14.92$, $p<0.001$, $\eta^2=0.62$) (Figure 1). Post hoc paired t-test between day 1 and our predefined outcome at 2-week follow-up confirmed the hypothesis that HDRS-17 scores at 2-week follow-up (M=6.6, SD=2.46) were

FIGURE 2. Individual alpha frequency (IAF) power change[a]



[a] Left: percent reduction in average individualized alpha frequency (IAF) Power over treatment days; EEG was measured before application of CL-tACS. IAF power was significantly reduced at Day 4 compared to Day 1; right: correlation of percent change in IAF power at Day 4 and HDRS-17 score at 2-week follow-up. The change in IAF power correlated significantly with MDD severity. * < 0.005

significantly lower than at day 1 (M=18.2, SD=3.94), p<0.001, d=3.27. Importantly, quality of life improved over time (Q-LES-Q-SF, F[3,27]=19.07, p<0.001, η^2=0.68) with significant improvement at 2-week follow-up (M=57.86, SD=10.25) from day 1 (M=39.82, SD=5.77), p=0.002, d=2.28. Overall, following the completion of a 5-day course of CL-tACS, we observed an 80% response rate and an 80% remission rate 2 weeks post-treatment.

EEG Results

As hypothesized, pre-treatment IAF power significantly decreased during the treatment week (F[4,36]=2.88, p=0.036, η^2=0.24). Post hoc analyses showed a significant reduction in IAF power at day 4 (M=−28.21%, SD=27.41), t (9)=−3.26, p=0.01. This reduction was partially maintained at day 5 (M=−21.96%, SD=34.64), t (9)=−2.01, p=0.076. Correlation analyses revealed that the decrease in IAF power at day 4 was significantly correlated with reduction in symptom severity (HDRS-17) at 2-week follow-up, (r [9]=0.894, p<0.001) (Figure 2). The daily fluctuation in IAF was subtle and IAF did not systematically change during the course of treatment (F[4,36]=1.3, p=0.289, η^2=0.13).

Side Effects and Adverse Events

On average, participants rated all 12 side effect items after CL-tACS as "absent" or "low." One participant experienced nausea and vomiting during the first treatment session. These transient symptoms were mild and considered unlikely to be related to stimulation since the participant did not disclose an ongoing COVID-19 infection, which included headache, dizziness, and nausea before stimulation onset. Study participation was ended for this participant. No serious adverse events occurred.

DISCUSSION

We report results from the first clinical trial administering individualized CL-tACS to people with MDD. Two weeks after the 5-day CL-tACS intervention at IAF, HDRS-17 scores were significantly reduced, remission rate was 80% and quality of life significantly improved. Importantly, we further demonstrate successful target engagement (decreased alpha oscillations), as well as target validation (IAF power modulation correlated with depression severity at follow-up). The study is limited by its open-label design and the uncertainty about the magnitude of the contribution of non-specific effects to the outcome (13). However, we expect that reducing alpha oscillations was the primary mechanism of symptom improvement, given the observed positive correlation between oscillation power change and symptom severity. In addition, we successfully replicated previous studies that utilized standard 10 Hz-tACS in MDD and showed a reduction of alpha power (4, 9). Participants exhibited a moderate level of depression severity along with mild-to-moderate treatment resistance, indicating a lesser severity of illness compared to previous non-invasive brain stimulation studies (14). This observation holds implications for an upcoming randomized controlled trial with sufficient statistical power, which is required to confirm the superiority of CL-tACS over sham stimulation for the treatment of MDD.

CL-tACS offers novel avenues for personalizing brain stimulation for treating psychiatric illnesses by targeting pathological changes in brain network oscillations. Here we present highly promising preliminary data demonstrating the viability of IAF-based CL-tACS for the treatment of MDD. Following its successful validation in controlled studies, CL-tACS has the potential to become a safe, accessible, and effective non-pharmacological treatment option to fill the treatment gap and help alleviate the mental health crisis.

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