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Reduction in Left Frontal Alpha Oscillations by Transcranial Alternating Current Stimulation in Major Depressive Disorder Is Context Dependent in a Randomized Clinical Trial

Justin Riddle, Morgan L. Alexander, Crystal Edler Schiller, David R. Rubinow, and Flavio Frohlich

ABSTRACT

BACKGROUND: Left frontal alpha oscillations are associated with decreased approach motivation and have been proposed as a target for noninvasive brain stimulation for the treatment of depression and anhedonia. Indeed, transcranial alternating current stimulation (tACS) at the alpha frequency reduced left frontal alpha power and was associated with a higher response rate than placebo stimulation in patients with major depressive disorder (MDD) in a recent double-blind, placebo-controlled clinical trial.

METHODS: In this current study, we aimed to replicate successful target engagement by delineating the effects of a single session of bifrontal tACS at the individualized alpha frequency (IAF-tACS) on alpha oscillations in patients with MDD. Eighty-four participants were randomized to receive verum or sham IAF-tACS. Electrical brain activity was recorded during rest and while viewing emotionally salient images before and after stimulation to investigate whether the modulation of alpha oscillation by tACS exhibited specificity with regard to valence.

RESULTS: In agreement with the previous study of tACS in MDD, we found that a single session of bifrontal IAF-tACS reduced left frontal alpha power during the resting state when compared with placebo. Furthermore, the reduction of left frontal alpha oscillation by tACS was specific for stimuli with positive valence. In contrast, these effects on left frontal alpha power were not found in healthy control participants.

CONCLUSIONS: Together, these results support an important role of tACS in reducing left frontal alpha oscillations as a future treatment for MDD.

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The left prefrontal cortex is recruited during the processing of positive emotions (1), and this region has been found to be inhibited, indexed by increased alpha-frequency power, during the processing of positive emotions in individuals with depression (2) and preclinical dysphoria (3). Thus, noninvasive brain stimulation interventions for major depressive disorder (MDD) targeted the left frontal cortex with the goal of increasing neural activity (decreasing alpha) (4–6). However, the first transcranial magnetic stimulation protocol that was approved by the Food and Drug Administration for the treatment of depression delivered pulse trains to left prefrontal cortex in the alpha frequency (10 Hz) (7,8). This approach is counterintuitive because alpha-frequency electrical activity is inhibitory to neural activity (9). Nonetheless, the treatment approach was successful, which led to the theory that amplifying pathological activity (i.e., further increasing alpha power) may cause a homeostatic rebound that results in reduced alpha power after stimulation (10).

We recently performed the first randomized controlled trial of transcranial alternating current stimulation (tACS) in patients with MDD in which we delivered synchronized alpha frequency (10 Hz) current to left and right prefrontal cortex (11). We found that 4 consecutive days of stimulation produced a lasting decrease in left frontal alpha power in the eyes-open, resting state, compared with baseline. These findings are consistent with the interpretation that stimulation disinhibited activity in the left frontal cortex. However, this initial study was conducted with a small sample size (n = 18 for relevant conditions) and only in patients with MDD. Despite the preregistered successful change in the targeted left frontal alpha oscillations, the lack of understanding how and when homeostatic network reorganization occurs makes this finding counterintuitive. Thus, to better understand the immediate impact of tACS on left frontal alpha oscillations, we conducted a double-blind, parallel-arm, placebo-controlled clinical trial in patients in a major depressive episode (MDE) (n = 41) and with an age- and sex-matched control group (n = 41) in which we delivered 40 minutes of tACS targeted to bilateral frontal cortices and recorded eyes-open, resting-state electroencephalography (EEG) before

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and after stimulation. The frequency of stimulation was personalized by identifying and targeting the individual alpha frequency (IAF). By matching the stimulation frequency to the peak frequency of endogenous activity for each individual, we hypothesized that the ability of tACS to modulate brain activity would be increased (12). The primary outcome measure was a reduction in left frontal alpha oscillations with verum stimulation relative to sham for patients in an MDE (NCT03449979). In addition, participants passively viewed emotional images from the International Affective Picture System (IAPS) before and after stimulation. Because elevated amplitude of left frontal alpha oscillations is theorized to correspond to a reduction in approach toward positive experiences (1,2), we hypothesized that stimulation may produce a selective decrease in left frontal alpha oscillations to images rated as positive. The addition of an emotional context provided the ability to investigate whether the impact on left frontal alpha oscillations was context dependent. Furthermore, the inclusion of a control group allowed us to determine whether tACS effects on left frontal alpha oscillations are specific to depression or whether simulation produces a rebound effect in all participants. Finally, recent evidence indicates that hyperconnectivity in prefrontal cortex may index depression severity (13–17). In an exploratory functional connectivity analysis, we attempted to replicate this finding that would lend further insight into our strategy of synchronizing the left and right prefrontal cortex with synchronized stimulation.

METHODS AND MATERIALS

The experiment was approved by the Institutional Review Board at the University of North Carolina at Chapel Hill. Participants recruited from the Raleigh-Durham-Chapel Hill community provided written consent before participation. The experiment was conducted in the Carolina Center for Neurostimulation from September 2018 to August 2019. The experimental design consisted of two groups, those in an MDE and euthymic control participants, in which each participant received either tACS or an active sham stimulation in a parallel-arm design to improve participant blinding and because depression is often episodic and symptoms change over time (see the CONSORT diagram in Figure S1). The experiment was preregistered on ClinicalTrials.gov, where the complete protocol can be found (NCT03449979). First, eyes-closed, resting-state EEG was acquired at the start of the experiment. These data were used to determine IAF (Figure 1A), which was used as the frequency for tACS (Figure 1B). Second, participants performed a streamlined version of the Expenditure of Effort for Reward Task; these results are reported in a different study (18). Third, participants passively viewed images from the IAPS while EEG was acquired. Fourth, eyes-open, resting-state EEG

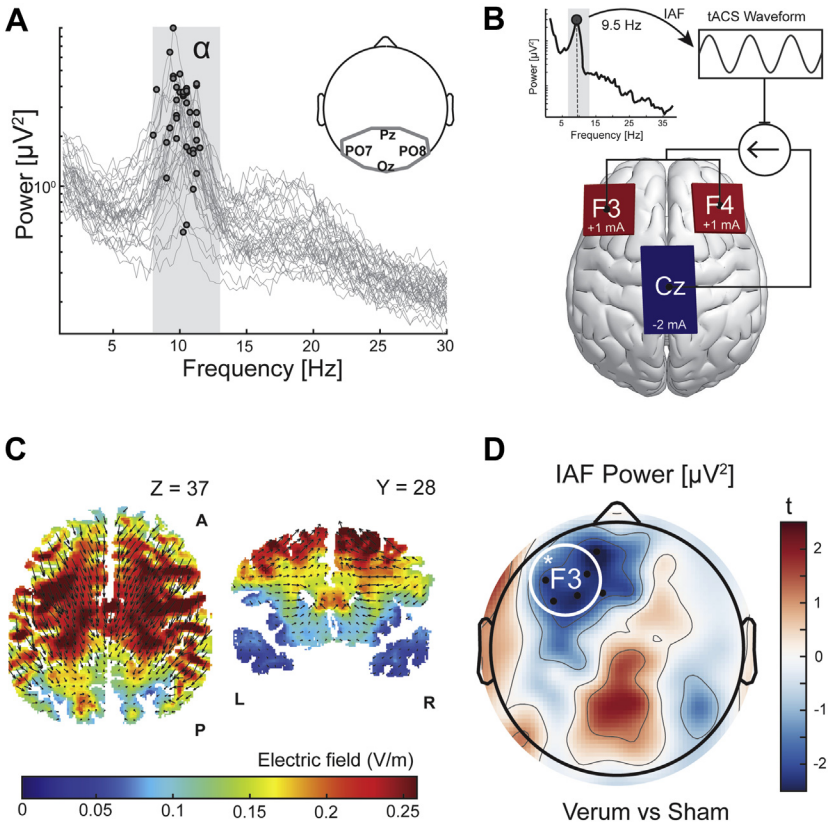

Figure 1. Individual alpha frequency (IAF)–transcranial alternating current stimulation (tACS) decreased left frontal IAF power in patients with major depressive disorder. **(A)** IAF was localized using an eyes-closed, resting-state electroencephalography. The power spectrum from occipital-parietal electrodes (outline of region of interest shown in insert) for each participant is depicted. The frequency with maximum power within the alpha band from 8–13 Hz (labeled gray box) is denoted with a black circle for all patients in the major depressive disorder group. **(B)** After localizing IAF for each participant, tACS was applied to the scalp at IAF. A hypothetical participant is depicted. Dotted line shows the IAF with maximum power in the gray rectangle of the canonical alpha band. IAF-tACS delivered identical current at 1-mA zero-to-peak with a split-wire to two 5 × 5-cm stimulator pads on the left and right frontal cortices (over F3 and F4). The 5 × 7-cm return stimulator pad over Cz acted as an electrical sink. **(C)** Electric field model shows the regions with maximum electric field strength (V/m) and depicts the electric force lines. On the left, an axial view at the +37 z-plane of Montreal Neurological Institute space orientated anterior (A) to posterior (P). On the right, a coronal view at the +28 y-plane of Montreal Neurological Institute space orientated left (L) to right (R). **(D)** IAF-tACS produced a selective decrease in IAF power for verum vs. sham (modulation index) over the left frontal region of interest (white circle). *$p < .05$. Electrodes with a significant change are depicted with black dots, $p < .05$, that were in a cluster of at least three contiguous significant electrodes.

was acquired just before the start of IAF-tACS. During stimulation, EEG was not collected, as these data are corrupted by the stimulation waveform. Immediately after IAF-tACS, eyes-open, resting-state EEG was recorded followed by passive viewing of novel images from the IAPS. Finally, previously viewed emotional images were presented a second time in a random order, and participants provided a subjective rating of their emotional reaction to each of the images.

Participants and Assessment of Depression Severity

Men and women, age 18–65 years, with normal or corrected-to-normal vision were recruited using advertisements in the community. Potential participants completed a brief phone screening, and 126 participants were enrolled in the experiment (Figure S1). After applying inclusion and exclusion criteria (Supplement), 84 participants were randomized to receive either IAF-tACS or sham-tACS, and 82 participants were included in the final analysis (66 women): 41 healthy control participants and 41 patients in an MDE (38 with MDD, 2 with bipolar disorder, and 1 with a premenstrual dysphoric disorder preliminary-diagnosis). We refer to these patients as the MDD group for simplicity, but we included all participants in subsequent analyses. Our analyzed sample size goal was at least 80 participants, which was determined to exceed $1 - \beta > 0.95$ based on the large effect-size on left frontal alpha power in our previous clinical trial with this stimulation montage in the same study population (11). In each group, 21 participants received verum stimulation (17 women), and 20 participants received an active sham (16 women). Depression severity was quantified using the Hamilton Depression Rating Scale and Beck Depression Inventory-II and was used in individual differences analyses. Descriptive statistics for the patients in the MDD group and healthy control population are reported in Table 1, and demographic information for patients in the MDD group is reported in Table 2.

Preprocessing of the Electroencephalogram

EEG data were collected with a high-density 128-channel electrode net at 1000 Hz (HydroCel Geodesic Sensor Net; Electrical Geodesics, Inc.) and EGI system (NetAmps 410; Electrical Geodesics, Inc.). The impedance of each electrode was below 50 kΩ at the start of each session. Because tACS was delivered using three conductive electrodes of sizes 5 × 5 cm to F3 and F4 and 5 × 7 cm to Cz, electrodes around these regions were bridged. The Cz electrode, which served as the reference electrode in the EGI system, was placed directly on the scalp via a hole cut in the stimulation electrode surrounding Cz. A typical preprocessing pipeline was used for the EEG data during resting-state and emotional image viewing [e.g., (19,20)] (Supplement).

Transcranial Alternating Current Stimulation

The electrode montage for tACS was adapted from our previous randomized clinical trial of MDD (11). However, in our previous experiment, stimulation was delivered at a fixed frequency in the canonical alpha band (10 Hz). Here, stimulation was delivered at the IAF, because previous work demonstrated that stimulation is able to more effectively entrain neural activity to the stimulation waveform when matched to the frequency of the targeted neural activity (12,21). To localize IAF, we recorded 2 minutes of eyes-closed, resting-state EEG before any other recordings. These data were analyzed during the acquisition of task data (Figure S1) using an abbreviated preprocessing pipeline (Supplement) and used for stimulation and subsequent analysis of resting-state EEG data. IAF was derived from parietal-occipital electrodes, and this frequency was comparable to IAF derived from left frontal electrodes (Figure S2). IAF-tACS was delivered using a lightweight battery-powered device with a paired tablet that was designed for double-blind clinical trials (XCSITE 100; Pulvinar Neuro LLC) using the same protocol as in our previous study (11) (Supplement). The induced electric field from stimulation was estimated using the ROAST toolbox on a template brain (22). Electric field models showed that current flowed primarily in the anterior-posterior orientation (Figure 1C).

Spectral Analysis

Spectral analysis was run on the 4-minute eyes-open, resting-state EEG data before and after stimulation using the fast Fourier transform on every 2-second epoch with no overlap. Median power spectra were calculated, and IAF ± 1 Hz was averaged for each channel. IAF power was normalized within each participant by dividing each channel by the sum of the 90 channels on the scalp. In our previous experiment, alpha power in left frontal electrodes showed the strongest modulation from stimulation. Thus, our primary analyses were performed on left frontal electrodes (F3 and the five surrounding electrodes) to reduce multiple comparisons in a preregistered analysis. An exploratory search of the scalp was performed to

Table 1. Descriptive Statistics for Patients in the Major Depressive Disorder Group and for Age- and Sex-Matched Healthy Control Participants

	Major Depressive Disorder Group (n = 41)		Healthy Control Group (n = 41)	
Metric	Mean	SD	Mean	SD
Age, Years	28.0	11.9	27.6	11.9
Beck Depression Inventory-II Score	26.3	9.2	2.0	2.4
Hamilton Depression Rating Scale Score	17.0	4.0	2.0	1.9
Individual Alpha Frequency	10.2	0.8	10.0	0.7

Individual alpha frequency (IAF) was calculated with minimal preprocessing during the experiment from parietal-occipital electrodes. The resolution of IAF was 0.5-Hz resolution. IAF was used for stimulation and for subsequent analysis of stimulation effects on resting-state electroencephalography data.

Table 2. Descriptive Information Specific to Patients in the MDD Group (n = 41)

	Verum (n = 21)	Sham (n = 20)
Beck Depression Inventory-II Score	25.09 (9.20)	27.55 (9.25)
Hamilton Depression Rating Scale Score	16.43 (4.19)	17.65 (3.79)
Education[a]	2.67 (0.97)	2.50 (0.83)
Depression Occurs in Episodes (Instead of Continuously)	15 of 21	17 of 20
Duration of current episode, months[b]	3.00 (2.93)	2.00 (13.95)
Maudsley Staging Method Score	6.28 (2.08)	6.25 (1.97)
Medication for Mood Disorder in the Last Year	10 of 21	12 of 20
Medication for Mood Disorder in the Last 2 Weeks	8 of 21	9 of 20
Current medication: SSRI	7 of 7	6 of 9
Current medication: NDRI	3 of 7	2 of 9
Current medication: Other[c]	1 of 7	3 of 9
Psychotherapy in the Last Year	15 of 21	10 of 20
Psychotherapy in the Last 2 Weeks	7 of 21	6 of 20
Comorbid Anxiety Disorder	12 of 21	11 of 20
Smoke Tobacco: Yes (Average Cigarettes per Week)	1 of 21 (5.00)	2 of 20 (0.75)
Drink Alcohol: Yes (Average Drinks per Week)	11 of 21 (2.81)	15 of 20 (2.57)

Values are mean (SD) or n unless otherwise indicated.
MDD, major depressive disorder; NDRI, norepinephrine-dopamine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.
[a]For education level, 1–5 is some high school, high school, some college or associates degree, bachelor's degree, advanced degree.
[b]Median and median absolute deviation used owing to outliers.
[c]"Other" includes buspirone, trazodone, brexpiprazole, and amitriptyline.

understand the spatial specificity of significant effects. The change in IAF power from IAF-tACS was calculated using the modulation index $\frac{post-pre}{pre+post}$ to normalize for differences in the magnitude of IAF power between participants.

Functional Connectivity

In an exploratory analysis, functional connectivity analysis was run for IAF with a seed over left frontal cortex (F3) and a target in an a priori region of interest of right frontal electrodes (F4 and five surrounding electrodes) based on previous findings (16,17). Functional connectivity was calculated using weighted phase lag index. Channels surrounding F3—lateral to Fz and anterior to C3—were removed from the analysis, as connectivity with these channels exceeds the spatial resolution of EEG. The data for each recording was normalized by dividing each channel by the sum of all data channels, and the effect of stimulation was normalized using the modulation index.

Emotional Valence Task

Before and after stimulation, participants viewed emotionally salient images from the IAPS (23). In each of these sessions, 96 images were presented, with an equal number of each valence randomly interleaved (positive, neutral, and negative). Images were presented at fixation with a height of 10° visual angle. Participants were instructed to maintain fixation during image presentation and to blink during the intertrial interval. Each image was presented for exactly 2 seconds and was submitted to time-frequency analysis. At the end of the experiment, participants were presented with the same 192 images in a random order and asked to rate each image on a scale from 1 to 10, using the full scale, on how negative to positive the participant perceives the image to be (1 = very negative, 10 = very positive). The image-rating session was self-paced, and its EEG data were not analyzed.

We were interested in alpha power in the left frontal cortex during image viewing as a function of valence. Trials were categorized based on subjective rating collected at the end of the experiment. Positive images were rated 8–10 (number of trials was 39.5 ± 21.9), neutral was 4–7 (93.3 ± 34.1), and negative was 1–3 (59.2 ± 19.9). Two of the 41 patients in the MDD group did not have usable data because of technical errors. Four patients in the MDD group rated <5 images as positive. Thus, analyses for the positive condition comprised 18 patients in the MDD group who received verum and 17 who received sham. Time-frequency analysis was run by convolving trial data (mirrored to reduce edge artifacts) with five-cycle Morlet wavelets of 150 frequencies from 2 to 59 Hz spaced along an adjusted log scale in the following equation:

$$pwr = {}^{1}/_{freq^{0.05}}$$

This distribution approximated the naturally occurring power distribution of human brain activity (24). Data were averaged for each condition and baseline-corrected in time-frequency domain to −800 to −500 ms from image onset.

Statistical Analysis

To test for successful double-blinding, χ^2 tests of independence were run with stimulation type as group (verum or sham) and the guess made by the participant or experimenter as category. The α threshold was set at 0.05 with two tails for all statistical analyses. Our preregistered primary outcome was an interaction between time (before or after stimulation) and IAF-tACS (verum or sham) in the patients in the MDD group. Our follow-up analysis utilized the modulation index to normalize differences in magnitude of left frontal alpha

oscillations across patients. Multiple comparisons were reduced by preregistering our primary outcome, focusing on a single region of interest, defining a single time-frequency cluster from all trials in the emotional valence task [permutation-based cluster correction for mass (25)] and focusing on positive valence (3). Exploratory analyses include topographical analysis with a significance threshold of three significant contiguous electrodes, individual differences analysis using depression severity, IAF-tACS effect as a function of antidepressant use, the relationship of IAF functional connectivity between left and right prefrontal cortex with depression severity, and the impact of IAF-tACS in healthy control participants.

RESULTS

Electrical Stimulation Modulates Left Frontal Alpha Power in MDD

Participants were successfully blinded to the stimulation (n = 80, 2 participants did not answer, $\chi^2_{1,80} = 0.2631$, $p = .608$). Of the 42 participants who received verum stimulation, 33 believed that they received verum stimulation. However, of the 40 participants who received sham stimulation, 28 believed that they received verum stimulation (2 chose not to answer). Thus, participants, irrespective of stimulation type, were biased toward believing they received verum, and their accuracy was 53.8%, near chance levels. The experimenters were also blinded to stimulation (n = 82, $\chi^2_{1,82} = 0.038$, $p = .845$): accurate guessing for verum stimulation was 42.9% and 55.0% for sham stimulation. Thus, our double-blinding procedure was successful. Adverse events were common side effects of tACS and were found in 28.6% of participants for sham stimulation and 50% for verum stimulation.

Our primary outcome was an interaction between time and stimulation for patients in the MDD group, which was found to have a trend-level effect ($F_{1,39} = 3.119$, $p = .0852$). By using the modulation index to normalize for differences in magnitude of the alpha oscillation across patients, we found that left frontal IAF power was significantly decreased for verum relative to sham stimulation in patients with MDD (n = 41, -0.016 ± 0.007; $t_{39} = -2.133$, $p = .039$, $d = 0.667$) (Figure 1D). Post hoc t tests on the impact of IAF-tACS on left frontal IAF power for verum and sham stimulation revealed a significant increase in IAF power with sham in patients in the MDD group (0.012 ± 0.024; $t_{19} = 2.191$, $p = .041$, $d = 0.489$) (Figure 2A) and a not significant decrease in IAF power with verum (-0.004 ± 0.024; $t_{20} = -0.802$, $p = .432$, $d = 0.175$) (Figure 2B). These results suggest that without verum stimulation, left frontal IAF power was increased, but this rise in power was negated by IAF-tACS.

Individual Differences in the Effect of tACS

We investigated whether greater depression severity in patients in the MDD group resulted in a stronger modulation of left frontal IAF power from IAF-tACS. Indeed, self-report (Beck Depression Inventory-II) correlated with modulation of left frontal IAF power (Fisher's z, difference in correlation, $z_{39} = 2.185$, $p = .029$) (Figure 3A). Similar to the mean effect, post hoc analysis found a significant relationship for sham stimulation, but not verum (Figure S3). However, we did not find a significant relationship using a clinician-administered assessment (Hamilton Depression Rating Scale) ($z_{39} = 1.405$, $p = .160$) (Figure 3B). An additional variable that might mediate the impact of IAF-tACS on left frontal alpha power is medication status. An exploratory analysis found that the impact of IAF-tACS on left frontal alpha power was strongest in patients using an antidepressant (Figure 4).

Stimulation Disinhibits Left Frontal Cortex With Positive Images

Before and after IAF-tACS, participants passively viewed positive, neutral, and negative images (Figure 5A). Across all valences, we found a robust decrease in alpha amplitude from 0.1 to 1.5 seconds after stimulus onset (Figure 5B) used in subsequent analyses (0.1–1.5 seconds; 8–12 Hz). As hypothesized, we found that the amplitude of left frontal alpha oscillations was elevated for positive relative to neutral images at baseline in patients in the MDD group (n = 35, 0.094 ± 0.210; $t_{34} = 2.663$, $p = .012$, $d = 0.450$) (Figure 5C). There was no significant difference for negative relative to neutral images in left frontal electrodes (n = 39, 0.055 ± 0.194; $t_{38} = 1.779$, $p = .083$, $d = 0.301$) (Figure 5D).

With IAF-tACS, we found a significant reduction in left frontal alpha power for positive images relative to sham in

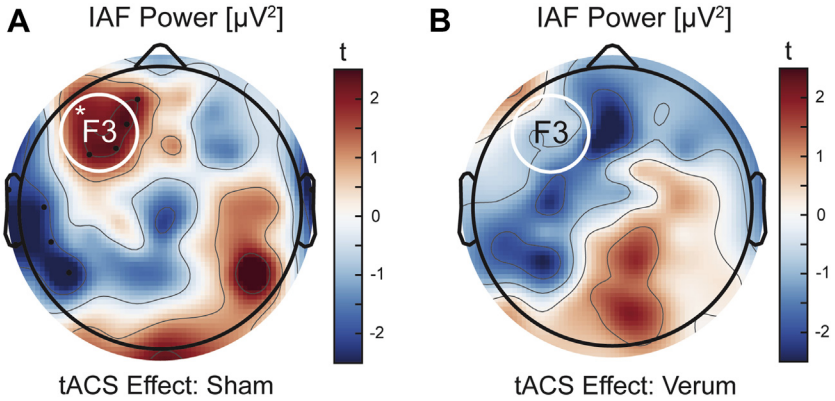

Figure 2. Individual alpha frequency (IAF)–transcranial alternating current stimulation (tACS) negated the increase in left frontal IAF power during the resting state. **(A)** In the absence of stimulation, a selective increase in IAF power over the left frontal region of interest (white circle) was observed. *$p < .05$. **(B)** Verum IAF-tACS did not produce a significant change in left frontal IAF power. Electrodes with a significant difference from post- to prestimulation are depicted with black dots, $p < .05$, that were in a cluster of at least three contiguous significant electrodes.

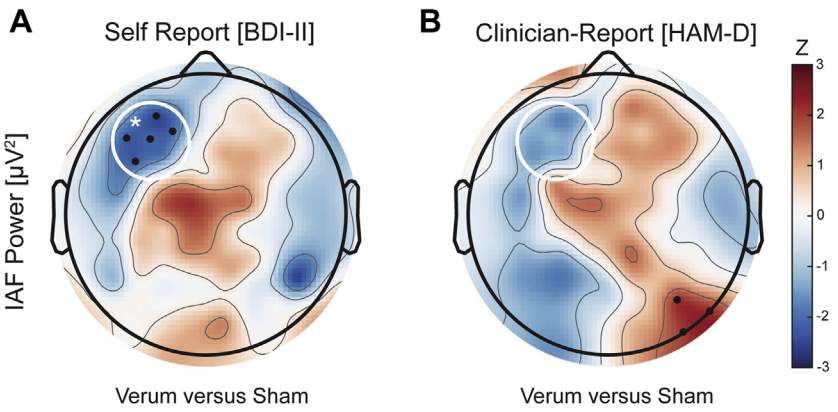

Figure 3. Individual difference in transcranial alternating current stimulation effect by depression severity. Individual differences in the impact of stimulation on individual alpha frequency (IAF) power across the scalp was correlated with baseline depression severity in patients in the major depressive disorder group quantified by self-report using the Beck Depression Inventory-II (BDI-II) **(A)** and clinician report using the Hamilton Depression Rating Scale (HAM-D) **(B)**. The difference in correlation between the verum and sham group found a focal difference in left frontal electrodes. Left frontal region of interest highlighted with a white circle. *$p < .05$. Dots represent electrodes with a significant difference and at least three contiguous significant electrodes.

patients in the MDD group (n = 35, −0.235 ± 0.113; t_{33} = −2.045, p = .049, d = 0.715) (Figure 5E) but no change in subjective ratings for positive images (n = 41, verum: 6.700 ± 0.780, sham: 7.020 ± 1.055, t_{38} = −1.089, p = .283, d = 0.348). Post hoc analysis of the impact of verum and sham stimulation separately revealed a nonsignificant decrease in alpha amplitude for verum (n = 18, −0.160 ± 0.405; t_{17} = −1.678, p = .112, d = 0.396) and no significant change for sham (n = 17, 0.075 ± 0.252; t_{16} = 1.221, p = .240, d = 0.296) (Figure 5F). While stimulation resulted in a decrease in left frontal alpha oscillations during eyes-open resting state, the decrease in left frontal alpha oscillations during the emotional valence task was specific to images rated as positive and was unchanged for images rated as negative or neutral (Figure S4).

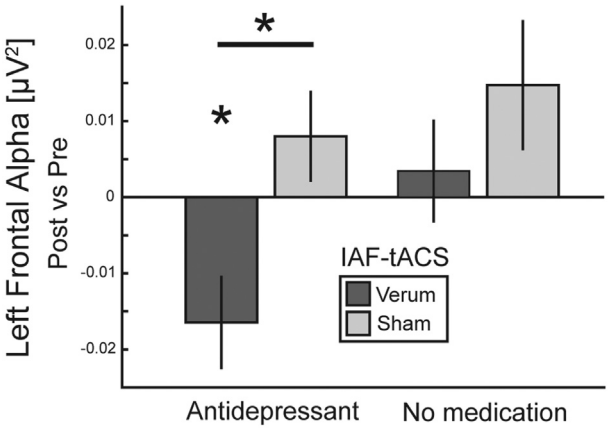

Figure 4. Analysis of the effect of individual alpha frequency (IAF)–transcranial alternating current stimulation (tACS) on left frontal IAF power by medication status. Patients in the major depressive disorder group were categorized by use of an antidepressant within the past 2 weeks. A two-way analysis of variance between antidepressant use and stimulation (verum or sham) found a main effect of stimulation ($F_{1,37}$ = 4.791, p = .035, η_p^2 = 0.11), a trend-level effect of antidepressant use ($F_{1,37}$ = 3.277, p = .078, η_p^2 = 0.08), and no interaction ($F_{1,37}$ = 0.801, p = .377, η_p^2 = 0.02). Post hoc testing revealed a significant effect of stimulation with antidepressant use (n = 17, t_{15} = −2.848, p = .012, d = 1.386) driven by a decrease in left frontal IAF power for verum (n = 8, t_7 = −2.683, p = .031, d = 0.949). Without antidepressants, there was no significant effect of stimulation (n = 24, t_{22} = −1.049, p = .305, d = 0.428). Critically, there was no difference in depression severity (Hamilton Depression Rating Scale) between patient groups by antidepressant use (t_{39} = 0.124, p = .902, d = 0.0398). *$p < .05$. Error bars are SEM; units are modulation index.

Healthy Control Participants Did Not Exhibit Left Frontal Alpha Modulation

To better understand the impact of IAF-tACS, we investigated whether healthy control participants exhibited the same increase in left frontal alpha power to positive imagery and to placebo stimulation. At baseline, healthy control participants did not exhibit an increase in left frontal alpha power to positive versus neutral images (2 participants did not have sufficient trials, n = 39, 0.014 ± 0.235, t_{38} = 0.379, p = .707, d = 0.061) (Figure 6A). Furthermore, healthy control participants did not show differential modulation of left frontal alpha power to positive images between verum and sham (n = 38, 0.001 ± 0.113, t_{36} = 0.013, p = .990) nor a reduction from verum stimulation (n = 19, 0.025 ± 0.296, t_{18} = 0.369, p = .716, d = 0.085) (Figure 6B). Furthermore, there was no change in left frontal IAF power during eyes-open resting state from stimulation (time by stimulation, $F_{1,39}$ = 0.187, p = .6676). Post hoc analyses did not reveal a significant difference in left frontal IAF power between verum and sham stimulation (n = 41, −0.003 ± 0.007, t_{39} = −0.423, p = .675) (Figure 6C) nor a significant increase from sham stimulation (n = 20, 0.006 ± 0.025, t_{19} = 1.109, p = .281, d = 0.248) (Figure 6D). Comprehensive analyses of variance performed across all participants for the eyes-open resting state recapitulated the pattern of findings revealed from our preregistered hypothesis-based statistical approach (Supplement).

Functional Connectivity, Not Power, as a Predictor of Depression Severity

As an exploratory analysis, we investigated a possible relationship between functional connectivity in IAF between left and right frontal cortex and depression severity (Hamilton Depression Rating Scale) in patients in the MDD group (baseline: 0.012 ± 0.010) and found a significant positive association (n = 41, r_{40} = 0.353, p = .024) (Figure 7A). By comparison, there was no significant relationship between left

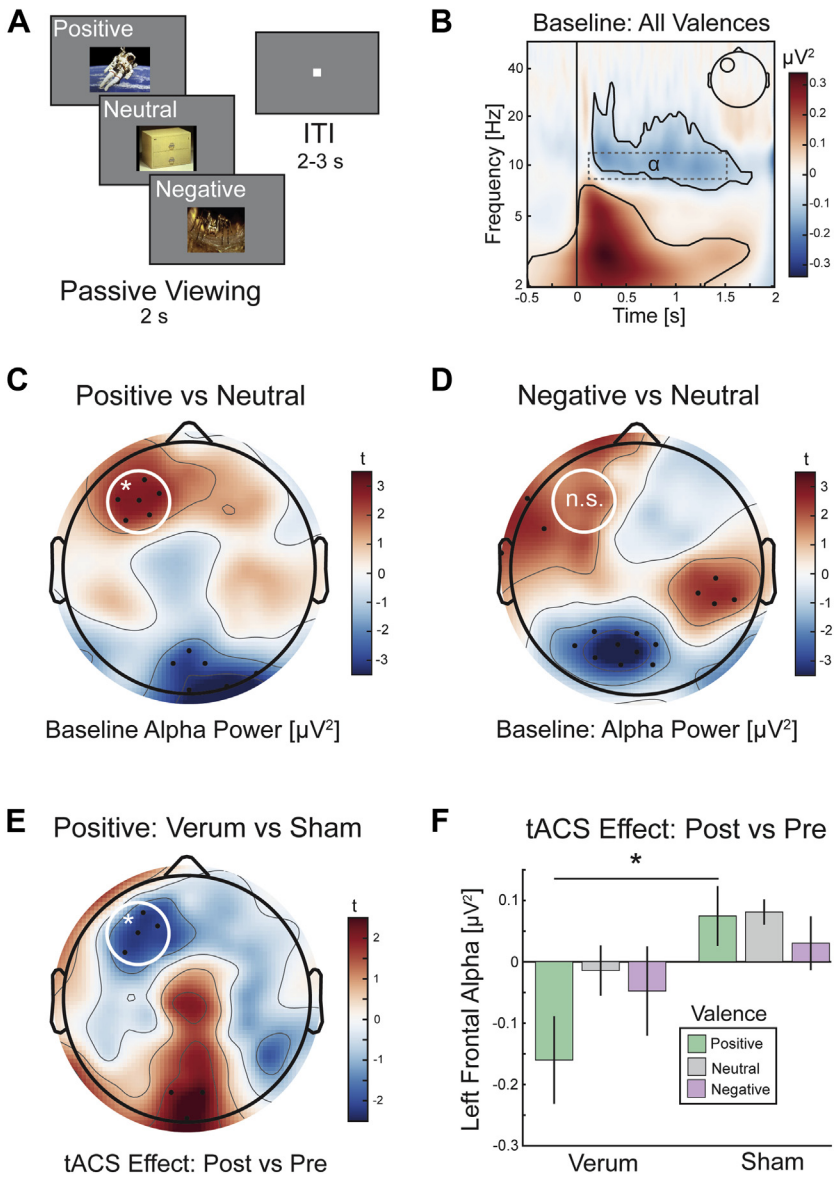

Figure 5. Elevated left frontal alpha power to images rated as positive is inhibited by individual alpha frequency–transcranial alternating current stimulation (tACS) in patients in the major depressive disorder group. **(A)** Patients passively viewed positive, neutral, and negative images from the International Affective Picture System (example images provided). Stimuli were presented for 2 seconds separated by a 2- to 3-second intertrial interval (ITI). **(B)** Across all valences at baseline in patients in the major depressive disorder group, time-frequency analysis revealed a significant decrease in alpha amplitude and increase in theta amplitude in left frontal electrodes (insert in the upper right). Black outline shows significant cluster at $p < .05$ after permutation-based cluster correction by mass. Vertical line at zero denotes onset of the image. The dashed gray rectangle from 0.1 to 1.5 seconds and 8–12 Hz is the alpha power that was extracted. **(C)** At baseline, the contrast of positive vs. neutral alpha power revealed a selective increase in left frontal electrodes and decrease in parietal-occipital electrodes. The white outline is the left frontal region of interest. *$p < .05$ for a priori analysis. Black dots represent electrodes with a significant difference that were in a cluster of at least three contiguous electrodes. **(D)** At baseline, the contrast of negative vs. neutral alpha power revealed no modulation in the left frontal region of interest (white circle). **(E)** For the contrast of verum vs. sham, there was a selective reduction of left frontal alpha power for positive images. The tACS effect is the change in alpha amplitude for image viewing data post-stimulation minus prestimulation. **(F)** For the left frontal region of interest, the change in alpha power from stimulation is shown for all valence and stimulation conditions. The comparison of interest from the baseline analysis revealed a significant difference for verum vs. sham. *$p < .05$. Error bars are within-participant SEM. Alpha power was *z*-transformed across scalp electrodes, so units are *z*. n.s., not significant.

frontal IAF power (baseline: 0.009 ± 0.001) and depression severity ($r_{40} = -0.177$, $p = .268$) (Figure 7B). Unsurprisingly, there was no significant relationship between depression severity and IAF functional connectivity in healthy control participants ($n = 41$, $r_{40} = -0.025$, $p = .874$).

DISCUSSION

Patients in an MDE were recruited to receive 40 minutes of tACS in the IAF designed to reduce left frontal alpha oscillations. Electrophysiology was recorded before and after stimulation. In agreement with our previous clinical trial that applied 5 consecutive days of tACS in patients with depression (11), we found a selective decrease in left frontal IAF power for verum versus sham stimulation. The effect was driven by an increase in left frontal IAF power for sham stimulation that was negated by verum stimulation. Individual difference analysis demonstrated that the impact of stimulation of tACS on left frontal IAF power scaled with greater depression severity as measured by self-report. Furthermore, the effects were strongest in those taking antidepressants within 2 weeks of IAF-tACS. To understand the context-dependent nature of elevated left frontal alpha oscillations, participants viewed positive, neutral, and negative images from the IAPS. At baseline, patients in the MDD group showed elevated left frontal alpha response to positive images relative to neutral images. As a function of stimulation (verum vs. sham), patients in the MDD group showed a

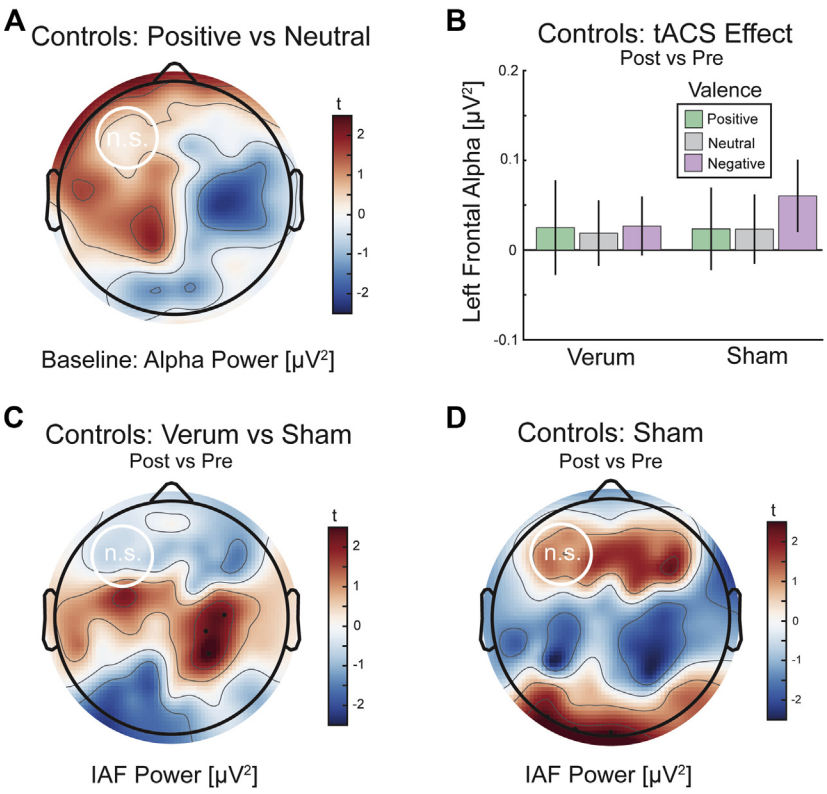

Figure 6. Healthy control participants without left frontal alpha engagement showed no effect of stimulation. **(A)** At baseline, there was no increase in left frontal alpha power for positive relative to neutral images. White circle depicts left frontal region of interest. **(B)** Left frontal alpha power did not show modulation from individual alpha frequency (IAF)–transcranial alternating current stimulation (tACS) in healthy control participants. Error bars are within-participant SEM. **(A, B)** Units are *z*-transformed alpha power values across scalp channels. **(C)** Control participants did not exhibit an impact of IAF-tACS for verum vs. sham in left frontal IAF power. **(D)** Unlike the patients in the major depressive disorder group, healthy control participants did not show an increase in left frontal IAF power during resting state after sham stimulation, as in patients in the major depressive disorder group. Black dots depict $p < .05$ with at least three contiguous electrodes. **(C, D)** Units are modulation index. n.s., not significant.

reduction in left frontal alpha power in response to positive images. Together, these findings suggest that left frontal alpha power inversely tracks with approach toward positive experiences. Healthy control participants failed to show an increase in left frontal alpha either to positive images or during resting state with sham stimulation, and thus there was no effect of stimulation as there was no oscillopathy to negate. As an exploratory analysis, clinician-rated depression severity correlated positively with IAF functional connectivity strength between the left and right frontal cortices. Altogether, stimulation that delivers synchronized current to bilateral prefrontal cortex may disinhibit the left frontal cortex to approach positive experiences in patients with MDD.

The finding that verum stimulation did not have any impact on left frontal alpha in the presence of negative or neutral images suggests the importance of assessing cognitive and emotional state. Our previous clinical trial relied solely on an analysis of resting-state data. While the impact of stimulation was discernible and replicated in this study, the interpretation for how that activity relates to cognition or experience was inherently limited. By including conditions with emotionally salient images, the dynamic reaction of the brain was highly

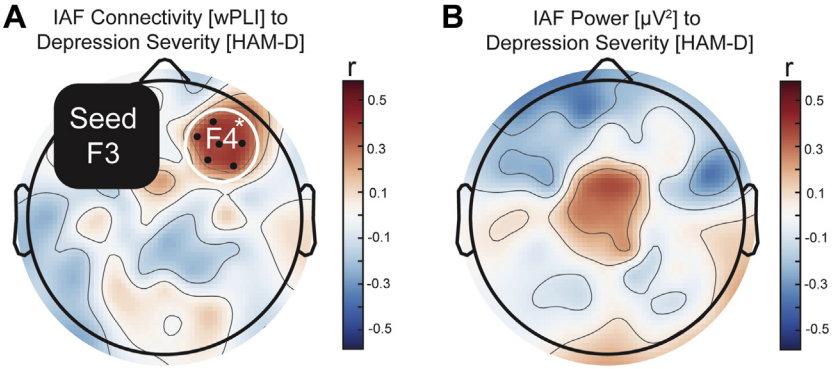

Figure 7. Individual difference in baseline functional connectivity positively tracked with depression severity. **(A)** Individual differences analysis revealed that depression severity (Hamilton Depression Rating Scale [HAM-D]) was positively correlated with functional connectivity strength (weighted phase lag index [wPLI]) between the left and right frontal cortices in patients in the major depressive disorder group. The artifact zone surrounding the seed in F3 is depicted with a black box with rounded corners. A dot here denotes an electrode with a correlation of $p < .05$ and with at least three contiguous significant electrodes. A white outline was drawn around F4 and the surrounding electrodes. **(B)** Individual differences analysis for individual alpha frequency (IAF) power did not reveal any significant relationship with depression severity in patients in the major depressive disorder group. Functional connectivity and IAF power values were divided by the sum of scalp channels.

informative, as positive images, but not negative or neutral images, resembled the eyes-open resting state. These findings suggest that the affective state of the participant is critical. Thus, systematic differences between laboratory environments could theoretically alter neural activity during resting state, which may explain failures to replicate for alpha-frequency power-based analyses, e.g., frontal alpha asymmetry in depression (26). Finally, we speculate that increased left frontal alpha power with sham stimulation may reflect the onset of apathy during the stimulation period, characteristic of deficits in motivation often seen in anhedonic depression (27,28).

Hypoactivation of the left prefrontal cortex has been a rather consistent finding in depression research, often associated with behavioral activation, or the pursuit of experiences that are deemed to be rewarding (27,29–33). Investigations with patients with MDD performing reward-based decision-making tasks have consistently found impairments in reward learning and motivation (34–36). These deficits may be dependent on impaired left prefrontal cortical activation (34), in which case IAF-tACS could be applied to improve reward learning or goal-directed behavior that in turn would alleviate symptoms of depression (37). Combining noninvasive brain stimulation with psychotherapeutic interventions that foster the pursuit of value-based, positive activities such as behavioral activation may be of clinical utility (38).

As with any scientific investigation, the present study has limitations. First, we did not measure levels of subjective arousal to the IAPS images. Thus, we cannot rule out a systematic difference in arousal for the positive versus the neutral and negative images. However, positive and negative images tend to evoke higher arousal than neutral images (39). Thus, the specificity of our stimulation effects to the positive imagery is not likely explained by arousal differences. Second, we could not record electrophysiology during stimulation (40,41), so we cannot confirm whether differences in neural entrainment to the stimulation waveform drove our effects. Finally, our experiment was not designed to systematically investigate additional important factors that might mediate the efficacy of stimulation such as medication class, treatment resistance, or demographic factors.

These findings are consistent with the homeostatic theory for targeting oscillopathy (10), in which the pathology is increased with stimulation to engage a biological reset. Future work is required to establish what qualifies as a maladaptive oscillation, leading to an oscillopathy, and whether some inherent quality makes this type of neural activity susceptible to homeostatic reset. This model is challenged by the fundamental difficulty in defining what is maladaptive, as the argument could be made that the system is precisely optimized but toward a maladaptive goal state. An alternative model is that stimulation delivered in an inhibitory band (e.g., alpha or beta band) drives a network reconfiguration, whereas stimulation delivered in an excitatory band (e.g., theta or gamma) does not. A recent experiment that delivered stimulation targeted to inhibitory activity produced a decrease in behavioral performance and reconfigured the targeted network, whereas targeting excitatory activity improved performance and enhanced network activity (19). Furthermore, stimulation in inhibitory bands may disrupt cognitive processing during stimulation but might confer cognitive or mood benefits after network reconfiguration. For example, beta-frequency (20 Hz) stimulation to the hippocampal memory network during task performance caused disruption of associative memory (42), but 5 consecutive days of stimulation in beta-frequency produced a lasting improvement in associative memory when tested in a follow-up session (43). Future research should investigate the potential for noninvasive brain stimulation to disrupt maladaptive network activity by delivering stimulation in a frequency associated with neuronal inhibition and subsequent sessions to consolidate network changes (44).

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ClinicalTrials.gov: Single Session of tACS in a Depressive Episode (SSDE); https://www.clinicaltrials.gov/ct2/show/NCT03449979; NCT03449979.

ARTICLE INFORMATION

From the Department of Psychiatry (JR, MLA, CES, DRR, FF), Carolina Center for Neurostimulation (JR, MLA, FF), Department of Neurology (FF), Department of Cell Biology and Physiology (FF), Department of Biomedical Engineering (FF), and Neuroscience Center (FF), University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.

Address correspondence to Flavio Frohlich, Ph.D., at flavio_frohlich@med.unc.edu.

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