



Depression relief from cranial nerve stimulation tracked with decreased prefrontal alpha power and connectivity similar to prefrontal stimulation: an exploratory analysis

Dear Editor,

Major depressive disorder (MDD) is difficult to treat and many patients fail to respond to first-line pharmaceutical treatments [1]. The development of alternative treatment options represents a critical need, and there are recent advances in the domain of non-invasive [2,3] and invasive brain stimulation [4]. A persistent limitation to developing novel treatments is the inability to objectively track treatment response with a physiological measurement. Robust neural metrics that correlate with symptom severity and reduction would provide a gold standard for future research. Potential biomarkers that are accessible by non-invasive measurement with electroencephalography (EEG) are the amplitude of left prefrontal alpha oscillations and alpha-frequency functional connectivity between the left and right prefrontal cortex.

In our previous studies, prefrontal alpha oscillations were targeted by administering five-consecutive days of bifrontal alpha-frequency transcranial alternating current stimulation (tACS) in patients with MDD which resulted in a reduction of depression symptoms and a corresponding reduction in left prefrontal alpha amplitude [5]. Additionally, left-right prefrontal alpha connectivity correlated with depression severity in patients with MDD [6], and reduced connectivity tracked depression symptom reduction following alpha-tACS in patients with schizophrenia [7]. When targeting left prefrontal alpha power using closed-loop alpha-tACS, patients with MDD showed a reduction in depression symptoms and reduced left prefrontal alpha power [8]. Together, these findings suggest that left prefrontal alpha power and left-right alpha connectivity might be predictive of depression symptom reduction in MDD.

An open question is whether these biomarkers track with depression symptoms for interventions that do not directly target prefrontal alpha oscillations. To address this question, 18 participants were recruited for an EEG sub-study (NCT05178784) from a parent multi-site double-blinded randomized clinical trial (NCT04279522) for the treatment of MDD using an external Combined Occipital and Trigeminal Afferent Stimulation (eCOT-AS), a non-invasive wearable device. The eCOT-AS (Proliv Rx, Neurolief Ltd) is a novel investigational medical device intended for home use as an adjunctive treatment to pharmaceutical management in adult patients with MDD who failed to achieve satisfactory improvement from antidepressant medication treatment. Participants received active stimulation with the Proliv Rx device or an identical device that delivered sham stimulation, i.e., it did not provide a clinically relevant dose. The two study arms comprised 8 weeks of blinded treatment followed by an 8-week open label phase. The parent study found a significantly superior reduction in MDD symptoms for active relative to sham eCOT-AS (results are reported elsewhere; see Ref. [9]).

The EEG sub-study was approved by the Butler Hospital Institutional

Review Board (IRB) and conducted at two of the clinical study sites. For this sub-study, participants completed their first EEG session (EEG₁) prior to receiving eCOT-AS, their second (EEG₂) following the eight-week blinded phase, and their third session (EEG₃) after the eight-week open label phase. Symptoms of depression were measured with the 21-item Hamilton Depression Rating Scale (HAMD), Montgomery-Asberg Depression Rating Scale (MADRS), and Clinical Global Impression Scale for severity (CGI-S). During each EEG session, eyes-open resting-state EEG was collected. 12 participants were sampled at Butler Hospital and 6 at UCLA. After unblinding, it was revealed that 10 participants received verum (9 female; age 49.7 ± 14.2 ; HAMD-21 24.4 ± 3.6 ; MADRS 32.7 ± 5.5 ; CGI-S 5.2 ± 0.6) and 8 received sham (6 female; age 46.3 ± 15.4 ; HAMD-21 24.6 ± 3.5 ; MADRS 32.8 ± 3.7 ; CGI-S 5 ± 0). Of the 18 participants, 14 completed EEG₂ after the blinded phase, and 12 completed EEG₃ session after the open-label phase (Fig. 1A). In this small sample size, we ran a hypothesis-motivated exploratory analysis to investigate whether changes in left frontal alpha power and left-right alpha connectivity tracked with depression symptom improvement.

Verum eCOT-AS produced a significant reduction in symptoms of depression across all measures ($t_s < -2.6$, $p_s < 0.03$, $d_s > 0.89$), but this decrease was not significantly different from sham (HAMD-21: $t(13) = 0.94$, $p = 0.36$, $d = 0.49$; HAMD-17: $t(13) = 0.97$, $p = 0.35$, $d = 0.50$; MADRS: $t(13) = 0.68$, $p = 0.51$, $d = 0.35$; CGI-S: $t(13) = 0.78$, $p = 0.45$, $d = 0.40$) in this small subsample. Thus, our analysis was focused on individual differences in change of symptoms following intervention. With a sample size of 16, the primary analysis was powered only for large effect sizes, 68 % for an effect size of 0.55. For the EEG analysis (see Ref. [6] methods), we investigated EEG change associated with symptom reduction following the first exposure to 8 weeks of active stimulation, whether received during the blinded phase or during the open-label phase. Reduction in left prefrontal alpha power was positively related to decreased depression symptoms (Fig. 1B). This relationship was strongest to HAMD-21 (Fig. 1C). Topographic analysis revealed that the relationship was specific to the F3 electrode over left prefrontal cortex (Fig. 1D). Left-right prefrontal alpha connectivity was measured with weighted phase lag index (wPLI). We found a positive relationship between depression symptom reduction and connectivity reduction (Fig. 1E). This effect was strongest with MADRS (Fig. 1F). Topographic analysis revealed that the relationship was specific to left-right prefrontal connectivity between F3-F4 electrodes (Fig. 1G). As an exploratory analysis, left prefrontal alpha power and left-right prefrontal connectivity were correlated across individual at baseline and a significant positive relationship was discovered ($r(16) = 0.55$, $p = 0.02$, $CI = 0.11-0.81$).

Follow-up exploratory analyses were focused on those symptoms

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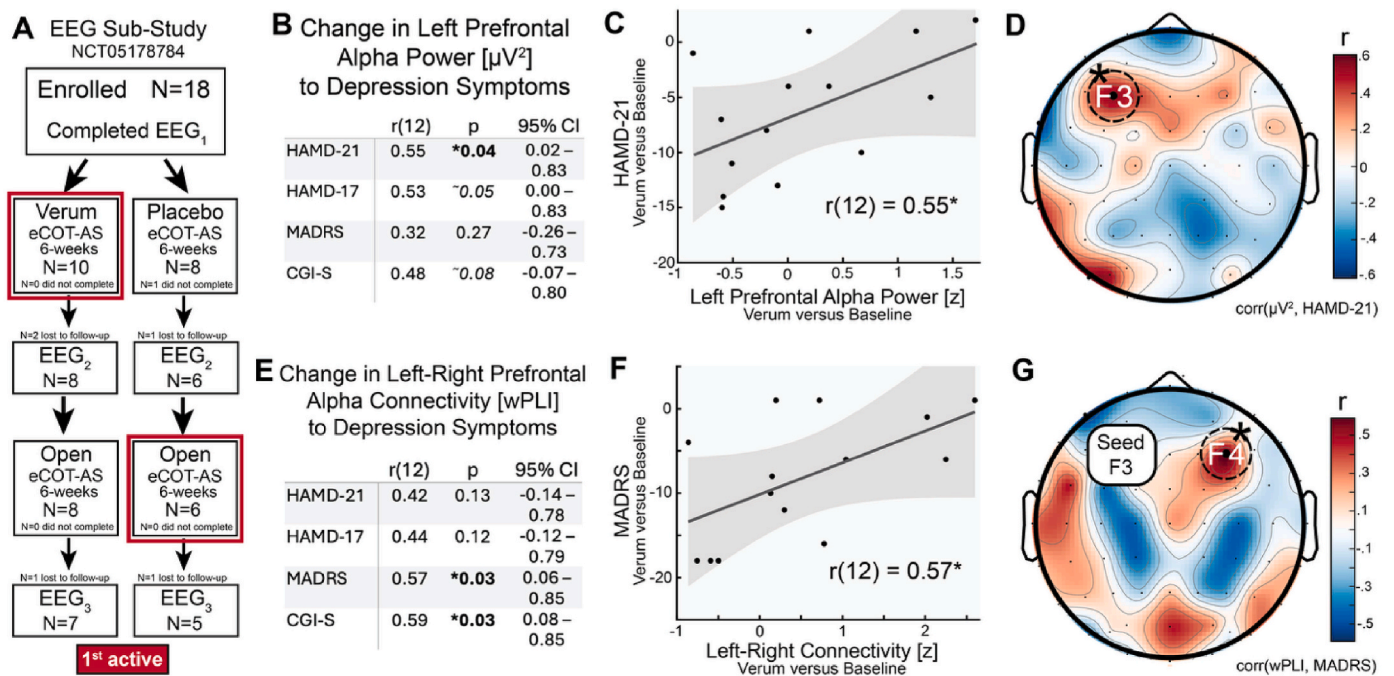


Fig. 1. (A) Flowchart showing the sub-study sample sizes and EEG data collection time points in relation to the blinded and open-label phases of the parent trial; boxes with a red boarder indicate sample and study phase where subjects had their first exposure to active stimulation. (B, C) Depression symptom reduction (HAMD-21) following active stimulation correlated with a reduction in left prefrontal alpha power. (D) Topographic analysis showed that the effect was specific to the left prefrontal cortex. (E, F) Response to combined occipital and trigeminal nerve stimulation correlated with a reduction in left-right prefrontal alpha connectivity. (G) Topographic analysis showed effects were specific to left-right connectivity. Shaded area is 95 % confidence interval. * indicates $p < 0.05$ in the a priori region of interest. Dashed circles show the hypothesized location of the effect based on our previous work. wPLI is weighted phase lag index.

with the strongest relationship to neural activity: HAMD-21 and MADRS. In participants that received sham (EEG₂ vs EEG₁), there was no relationship with left prefrontal alpha power (HAMD-21, $r(4) = 0.19$, $p = 0.72$, $CI = -0.73-0.87$; MADRS, $r(4) = 0.20$, $p = 0.70$, $CI = -0.73-0.87$) or left-right prefrontal connectivity (HAMD-21, $r(4) = 0.26$, $p = 0.62$, $CI = -0.70-0.88$; MADRS, $r(4) = 0.47$, $p = 0.35$, $CI = -0.56-0.93$). We investigated the impact of two consecutive active 8-week stimulation treatments (16 weeks) in a small subset of participant ($N = 7$) and found a consistent reduction in left-right prefrontal connectivity with symptoms (HAMD-21, $r(5) = 0.75$, $p = 0.05$, $CI = -0.02-0.96$; MADRS, $r(5) = 0.65$, $p = 0.11$, $CI = -0.21-0.94$). However, the reduction in left prefrontal alpha power from the first active treatment phase was not maintained following the second treatment phase (EEG₃ vs EEG₁; HAMD-21, $r(5) = -0.37$, $p = 0.42$, $CI = -0.88-0.53$; MADRS, $r(5) = -0.42$, $p = 0.35$, $CI = -0.89-0.49$). These findings suggest that left prefrontal alpha power might reflect initial treatment response but left-right prefrontal connectivity may reflect long-term changes in brain activity following treatment.

Our study is limited by its small sample size. Thus, the findings should be interpreted as exploratory with the intention to guide future investigation. While consistent in pattern, there was variability between different assessments of depression (HAMD-21 versus MADRS) that warrant future validation of these biomarkers are generalizable. The sample was predominantly female (83 %), which further constrains interpretations. Critically, prefrontal alpha dynamics might reflect emergent phenomena that track with depression treatment response, but do not mechanistically underlie the etiology of depression.

Overall, our exploratory analysis in a small sample size revealed that depression remediation with eCOT-AS reduced left prefrontal alpha power and left-right alpha connectivity despite engaging different neural mechanisms. Left-right prefrontal alpha connectivity was sensitive to long-term changes in depression severity, which is encouraging of future research to investigate this signal as a potential biomarker.

CRedit authorship contribution statement

Justin Riddle: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Eric Tirrell:** Data curation. **Lauren Hindley:** Data curation. **Andrew F. Leuchter:** Writing – review & editing, Funding acquisition, Conceptualization. **Flavio Frohlich:** Writing – review & editing, Funding acquisition, Conceptualization. **Linda L. Carpenter:** Writing – review & editing, Project administration, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest


JR has no competing interests to declare. FF is a shareholder of Electromedical Products International and receives payments from EPI for chairing the scientific advisory board, and is listed as an inventor on patents issued to UNC-Chapel Hill on non-invasive brain stimulation. AFL discloses that within the past 36 months, he has received research support from the National Institutes of Health, Department of Defense, Neuroptics, and NeuroSigma, Inc. He has served as a consultant to NeoSync, Inc., ElMindA, Options MD, and eFovea. LLC has received research support from Affect Neuro, Janssen Pharmaceuticals, Neuronetics, Neurolief, Nexstim, and SynapseBio, and she has served as a scientific adviser or consultant for Affect Neuro, Janssen Pharmaceuticals, Neuronetics, Neurolief, Nexstim, Otsuka, Sage Therapeutics, and Sunovion.

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