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Pioneering depression treatment with temporal interference stimulation: Intracranial and clinical evidence in humans

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Dear Editor,

Transcranial Temporal Interference Stimulation (TI) is a ground-breaking neuromodulation technique that has attracted considerable attention in recent years. Its core advantage lies in its unique ability to creatively and noninvasively modulate activity in deep brain regions. By applying two currents with different kHz frequencies (too high to drive neurons), TI generates a combined field modulated at the difference frequency low enough to cause neural activity.[1] This novel physical principle underpins its significant potential to revolutionize deep brain targeting. Recent studies have demonstrated that TI applied to healthy individuals can effectively regulate deep brain activity and enhance performance across various cognitive tasks.[2-4] Additionally, in patients with Parkinson's disease (PD), TI has shown promise in alleviating symptoms and abnormal deep region activity.[5,6] However, to date, there is a lack of direct physiological evidence confirming whether TI can successfully deliver stimulation into the deep regions of the living human brain, especially in comparison to surface areas. Meanwhile, Major Depressive Disorder (MDD), characterized by subcortical dysfunction, presents significant treatment challenges due to the limited ability of current neuromodulation techniques to effectively reach deep brain target. TI has shown promising but underexplored potential to overcome these limitations and meet clinical needs.

To fill these gaps, we conducted two independent experiments that are among the first to combine stereo-electroencephalographic (SEEG) recordings with TI stimulation, demonstrated that TI can effectively target deep brain regions and provided evidence for the potential of TI in treating MDD. This approach demonstrated the feasibility of TI in targeting MDD-relevant deep brain regions in the living human brain, and preliminarily evaluated its efficacy in alleviating depressive symptoms.

First, to provide direct evidence of TI stimulation generating expected envelope electrical field in deep brain regions, we leveraged SEEG electrodes clinically implanted in two patients with drug-resistant epilepsy (n=2; right-handed; aged 20–25 years; one female) at the Epilepsy Center of Ruijin Hospital, affiliated with Shanghai Jiao Tong University School of Medicine. The electrodes were implanted for clinical monitoring purposes. Real-time recordings of TI-induced electric fields were acquired from four MDD-related targets: the left dorsolateral prefrontal cortex (DLPFC), left subgenual anterior cingulate cortex (sgACC), right ventral striatum (VS), and right amygdala (Amg).[7-10] The depth electrode (5–20 contacts, 0.8 mm diameter, 2 mm each contact, 1.5 mm spacing, from Sinovation, Beijing, China or Rishena, Jiangsu, China or Alcis, Besancon, France) locations were based exclusively on clinical criteria and were verified by and post-implantation CT images fused with pre-implantation T1-weighted MRI. Based on the subjects' electrode locations, Patient 1 was selected to target the left sgACC (carrier frequency = 2 kHz, difference frequency = 100 Hz) in one session, and Patient 2 was selected to target the left DLPFC (carrier frequency = 2 kHz, difference frequency = 10 Hz), right Amg (carrier frequency = 2 kHz, difference frequency = 100 Hz), right VS (carrier frequency = 2 kHz, difference frequency = 100 Hz) in three separate sessions. Non-target contacts (on same depth electrode to include electrical noise obtained by each depth electrode, but farthest from target) served as controls. Target contacts were those closest to the region's center. For SEEG recordings, the raw voltage amplitude of SEEG followed the clinical settings and was referenced by a contact located near the skull. For TI stimulation, it was performed using four gold circular surface electrodes (1 cm outer diameter). Electrodes were placed directly onto the scalp beneath the head bandage patients wear, without interfering with implanted electrodes or clinical equipment. Ground electrode of TI stimulation was placed on the earlobe. Electrode impedance was kept < 7 kΩ. For each stimulation session, the protocols were determined a priori based on individualized electric field simulations conducted using Neurodome, aiming to solve the forward problem and optimize spatial targeting of the intended regions. During SEEG recording, a technical signal-scaling procedure was applied to ensure that the recorded TI-induced voltage signals remained within the dynamic range of amplifier and to avoid signal clipping. When the peak voltage exceeded the amplifier input range, the stimulation intensity was reduced by a fixed scale factor (1/10). This procedure was solely implemented for recording fidelity and did not reflect stimulation thresholding or participant tolerability. To extract the TI-induced electrical patterns, we applied a peak detection algorithm to ten-minute raw recordings from each channel. Peak and trough sequences were paired to eliminate noise fluctuations, and the envelope voltage was computed as the difference between each peak and its corresponding trough. Envelope modulation amplitude (mV) was defined as half of this peak-to-trough difference and was used to compare target and non-target contacts within each stimulation montage. To

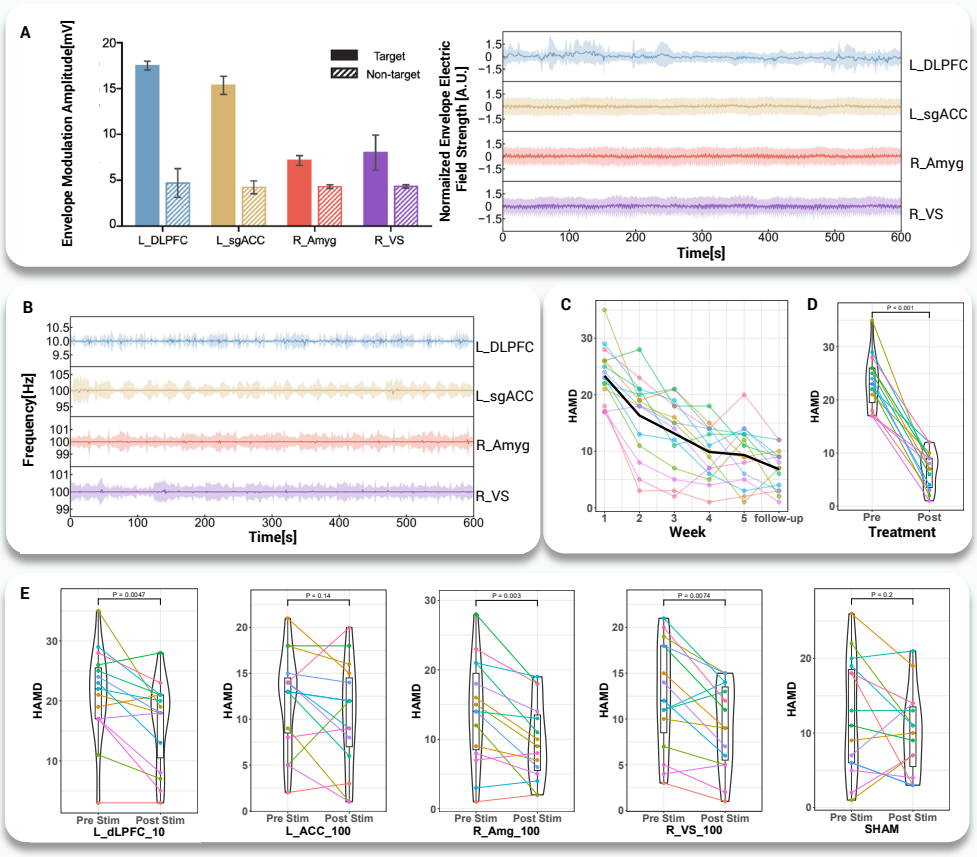

Figure 1. Intracranial EEG data by brain target (n = 2 epilepsy patients) and clinical outcome data (n = 15 MDD patients) (A) Left: Envelope voltages for four targets (vs. non-targets) induced by TI stimulation. Bar graphs represent mean and standard deviation of envelope voltages obtained in targets (solid) vs. non-targets (dashed) for the four brain regions of interest. Right: Normalized envelope electric field strength profiles obtained at target contacts across the four brain regions during the 10-minute TI stimulation session. Field strength values were normalized to the maximum value within each session and are shown in arbitrary units (A.U.) to illustrate the temporal stability and relative spatial gradients of the induced fields. (B) Envelope frequency obtained for each brain target during 10-min TI stimulation. (C) Trajectories of weekly assessed HAMD-17 for each participant. Group averaged HAMD-17 scores are depicted by the black bold line, colored lines indicate scores for individual participants. (D) Violin plot of HAMD-17 scores before and after 5-week treatment; the mean HAMD-17 score shows a significant decrease from pre- to post-treatment (one-tailed Wilcoxon test, $P < 0.001$). (E) Comparison of HAMD-17 scores between pre- and post-stimulation (with the pre-stimulation score referring to the score obtained one week after the stimulation and the post-score referring to the score obtained before the stimulation session taking place the next week). HAMD-17 scores for L_DLPFC, R_Amg and R_VS are significantly lower after stimulation (L_DLPFC, $P = 0.0047$; R_Amg, $P = 0.003$; R_VS, $P = 0.0074$); no significant score difference is present for L_sgACC ($P = 0.14$) and sham ($P = 0.2$). DLPFC, dorsolateral prefrontal cortex; sgACC, subgenual anterior cingulate cortex; Amg, amygdala; VS, ventral striatum.

assess spatial gradients of the induced field along the depth electrode trajectory, envelope electric field strength was defined as the difference of adjacent envelope voltage divided by the distance of these adjacent contacts and subsequently normalized for visualization purposes.

Using envelope modulation amplitude as a measure of target engagement, we observed consistently higher modulation amplitudes at target contacts compared with non-target contacts across all four stimulation montages (Figure 1A left; DLPFC = 17.50 ± 0.48 mV; sgACC = 15.35 ± 0.99 mV; Amg = 7.15 ± 0.53 mV; VS = 8.01 ± 1.92 mV; For corresponding non-targets: 4.68 ± 1.57 mV; 4.22 ± 0.71 mV; 4.29 ± 0.19 mV; 4.33 ± 0.19 mV), consistent with prior intracranial TI study (4). Envelope electric field strength estimates exhibited stable magnitudes over the stimulation period, with comparable values across subcortical targets (sgACC, Amg, VS) and higher values in the DLPFC (Figure 1A right; scaled to 1 mA current intensity for comparison; mean ± s.d.: DLPFC = 1.39 ± 0.13 V/m; sgACC = 0.12 ± 0.00 V/m; Amg = 0.20 ± 0.00 V/m; VS = 0.17 ± 0.01 V/m). Note that we only intend to validate the TI effect among these 4 targets, but not to compare the effect between the 4 targeted regions. The envelope frequency was derived by calculating the interval between consecutive peaks. The envelope frequencies were stable and matched the intended stimulation frequencies across all regions (Figure 1B; sgACC = 100.08 ± 0.11 Hz; Amg = 100.01 ± 0.09 Hz; VS = 100.01 ± 0.02 Hz; DLPFC = 10.01 ± 0.03 Hz). These findings provide the first direct physiological evidence that TI can reliably reach targeted deep brain regions with stable envelope frequency, supporting its potential as a noninvasive deep brain stimulation modality.

Building upon this evidence, we conducted the first pilot randomized, controlled, crossover clinical trial to evaluate the efficacy of TI in reducing depressive symptoms in patients with MDD (n = 15; mean age = 35.1 ± 10.9 years; 13 females, no participant changed their antidepressant medication regimen from 30 days prior to and throughout the study). Each participant received five 20-minute TI sessions over five consecutive weeks, one per week, in a randomized order covering five stimulation conditions: four active TI targeting the DLPFC (10 Hz), sgACC (100 Hz), Amg (100 Hz), and VS (100 Hz), and one sham stimulation condition. The procedure for TI was in line with SEEG study. The stimulation sites were based on subjects' TI-weighted MRI images and defined prior to TI. Four electrodes under a 10-10 system were selected for each TI target area. Stimulation intensity was individually adjusted using a titration procedure based on participant tolerability and subjective sensation thresholds, to minimize discomfort while maintaining blinding. For sham stimulation, we utilized current output without frequency difference to ensure blinding efficacy, and the electrodes were placed at arbitrary sites.

The results revealed significant reductions in depressive symptoms (assessed by the Hamilton Depression Rating Scale; HAMD) and anxiety symptoms (Hamilton Anxiety Rating Scale; HAMA) compared to baseline after the five-week intervention ($p < 0.05$; Figures 1C–D). Single-session analyses showed no significant symptom changes after sham stimulation. All active TI conditions, except sgACC stimulation, significantly reduced HAMD scores (Figure 1E), while stimulation of the DLPFC and Amg also significantly reduced HAMA scores. All participants completed the trial and reported only mild to moderate side effects, most commonly drowsiness and dizziness, following both active and sham stimulation sessions. These effects were possibly attributable in part to the 10-minute resting-state fMRI scans conducted before and after each stimulation session.

In summary, these findings collectively lay an important theoretical and clinical foundation for the use of TI as a novel non-invasive neuromodulation therapy for depression. Building upon existing evidence, the intracranial physiological evidence provided by our study directly demonstrates the feasibility of targeting deep brain regions. Importantly, we identified two promising therapeutic stimulation targets for MDD— the DLPFC and the right Amg. However, given the small sample size and the heterogeneity of our patient cohort, further validation in larger and more diverse cohorts is necessary. Meanwhile, although TI-induced amplitude-modulated electric fields were successfully delivered and enhanced in the targeted brain regions, some spillover to adjacent non-target regions was also observed (Figure 1A). While still in the exploratory stage, TI has already demonstrated its transformative potential as a non-invasive form of deep brain stimulation, offering new possibilities for treating MDD and other neuropsychiatric disorders. It also opens the door to multi-target, dynamic modulation strategies and may be applied to preoperative DBS target selection and response prediction. We look forward to future, more in-depth and long-term investigations to fully unlock its therapeutic potential in neuropsychiatric interventions.

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AUTHOR CONTRIBUTIONS

Junyi Yan handled TI data processing and drafted the manuscript. Shupei Zhou conducted participant evaluations. Yishu Chen oversaw TI operations and wrote the manuscript. Junjie Wang managed SEEG data. Simeng Zhang oversaw TI operations and adverse event recording. Fang Wang analyzed clinical data. Chengyu Pang contributed to study design and wrote the SEEG section. Wei Lu and Fan Wu recruited participants, while Qiangqiang Liu and Jiwen Xu assisted with SEEG. Lu Yang, Liankun Ren, Ines R. Violante, and Ulf Ziemann aided in data analysis and manuscript revision. Long Li, Xiaoqi Zhu, and Tian Liu simulated TI electric fields. Yong Lu, Hengfen Gong, Yiru Fang, and Chencheng Zhang led the study, interpreted data, and wrote the manuscript. All authors contributed to and approved the manuscript.

DECLARATION OF INTERESTS

Long Li, Xiaoqi Zhu, and Tian Liu, employees of Neurodome, were responsible for simulating the TI electric fields but did not participate in data analysis, or interpretation of results. The remaining authors have no competing interests to declare in relation to this study.

ETHICAL STATEMENT AND PATIENT CONSENT

The study obtained ethical approval from the local committee (PWRq2021-31). Written informed consent was obtained from patients after they were fully informed about the study's purpose and procedures.

DATA AND CODE AVAILABILITY

Data are available from the corresponding author (i@cczhang.org) upon reasonable request.