



Establishing naturalistic brain stimulation targeting aperiodic EEG features: Transcranial endogenous current stimulation (tECS)

Dear Editor,

Existing brain stimulation paradigms are based on synthetic waveforms, such as sinusoids, pulses, or band-limited noise [1,2], which capture only narrow features of neural activity. These overlook the rich temporal structure of endogenous neural electric fields, including the aperiodic 1/f component, transient bursts, cross-frequency interactions, and non-linear phase dynamics [3]. In contrast, a naturalistic (“endogenous”) stimulation waveform is one derived directly from EEG that retains this intrinsic spectral-temporal structure.

Weak electric fields recorded from cortical tissue can entrain local neuronal activity when applied to *in vitro* cortical networks [3], demonstrating that low-intensity, endogenous electric fields non-linearly shape neuronal network dynamics. This entrainment likely arises from rapid voltage transients that modulate voltage-gated Na^+ channels to enhance spike-timing precision even at low amplitudes [4]. At the circuit level, endogenous fields emerge from the interplay between excitatory pyramidal cells and inhibitory GABAergic interneurons, which maintain excitation/inhibition (E/I) balance [5]. On the macroscopic scale, the aperiodic exponent of the EEG power spectrum is used as a surrogate marker of E/I balance [6,7]. Reduced (flatter) exponents are thought to indicate increased cortical excitation, whereas steeper exponents represent greater inhibition [6,7] (Fig. 1A). E/I imbalance is increasingly linked to conditions such as autism and depression [8,9], yet its causal contribution remains unknown. Thus, recording endogenous electric fields, systematically manipulating the aperiodic exponent, and reapplying the edited waveform as ‘biomimetic’ stimulation enables perturbation of the macroscopic EEG signature associated with E/I balance. Approaches capable of perturbing E/I-related neural signatures could open a new, mechanistic route for intervention in clinical populations. Exploratory work in the sleep domain has piloted replaying EEG-derived cortical signatures during healthy sleep as stimulation to induce sleep-related brain states [10,11]. While this work demonstrates the feasibility of using EEG-derived signals for neuromodulation, it focuses on state replication via waveform replay, rather than controlled manipulation of specific neural signal properties to perturb defined neurophysiological targets.

Therefore, we developed transcranial endogenous current stimulation (tECS), a neuromodulation framework that uses an individual's EEG to generate endogenous stimulation waveforms that are parametrically modified to manipulate specific features of brain activity, such as the aperiodic exponent. By stimulating the brain with ‘edited’ waveforms similar to endogenous neural electric fields, tECS extends the principle first shown in cortical slices [3] to the human cortex (Fig. 1B).

In our open-label pilot, $n = 5$ healthy females aged 18–45 received five days of tECS aiming to increase cortical excitation at the Carolina Center for Neurostimulation (UNC-Chapel Hill). HD-EEG was recorded,

the aperiodic exponent was reduced (‘flattened’) by 50 %, and the edited EEG was delivered as a stimulation waveform. We applied the reduced-exponent tECS waveform in a tightly defined sample of women aged 18–45 to reduce variability in the small sample and to align with the target population of our forthcoming tECS trial in antenatal depression. tECS was delivered in 4×10 minute blocks (40 minutes total) for five consecutive days (Fig. S1) [2]. During stimulation, participants watched Reefscapes, a video of fish swimming in a coral reef, to standardize brain state [1,2]. The montage (F3/F4 [left/right prefrontal cortex; LPFC/RPFC], max 1 mA each, in-phase; and Cz [max 2 mA, anti-phase], applied using carbon-silicone electrodes with Ten20 paste [Fig. 1D]), matched our previous tACS clinical trials, targeting prefrontal networks implicated in depression [1,2]. Resting-state HD-EEG (eyes open) was recorded on Day (D)1 and D5 to assess neurophysiological changes. HD-EEG was also recorded daily immediately before and after stimulation blocks (Fig. 1E). A self-report stimulation sensation questionnaire was administered daily, immediately after stimulation, where participants were asked to rate ‘tingling/itching skin’, ‘warming skin’, ‘pressure on head’, and ‘flickering lights’ as ‘absent’, ‘low’, ‘medium’, or ‘high’. Any ‘high’ response was discussed with the study clinician (psychiatrist experienced in brain stimulation). If any sensations were rated as “high,” participants were asked whether this affected their ability to tolerate the stimulation. A response of “yes” informed possible classification of an adverse event by the clinician. We hypothesized that tECS would be safe (no serious adverse events), feasible (all participants recruited within defined study period and retained across the study period), and tolerable (all participants able to complete stimulation), and would show preliminary target engagement (change in aperiodic exponent between D1 and D5).

Personalized tECS waveforms were generated from baseline EEGs recorded within a week of the intervention (5 min, eyes open, watching Reefscapes). EEGs were preprocessed in EEGLAB (Supplementary Methods; Table S1). Personalized waveforms were derived from a 13-electrode F3-centered cluster, selected for its transdiagnostic role in executive and affective regulation [8,9]. Using the FOOOF toolbox [7] (2–40 Hz, fixed aperiodic mode), the aperiodic exponent was estimated (using Welch; mean fit $R^2 = 0.99$; exponent = 1.10 [range 0.96–1.32]), reduced by 50 %, then re-integrated with oscillatory components (using FFT; Supplementary Methods, Fig. S2 and S3, Table S2–S3). The reconstructed EEG signal (inverse FFT) was initially scaled to match the power of a 2 mA sine and then passed through a 400-step scale-and-clip search, finally selecting the largest scale factor for a ± 2 mA-clipped waveform preserving ≥ 0.95 spectral correlation with the original EEG. Final waveforms retained mean 82.12 % (79.50–85.0 %) of the RMS power of a 2 mA sine wave and closely matched the oscillatory frequency structure of the EEG (mean log-power spectral correlation $r =$

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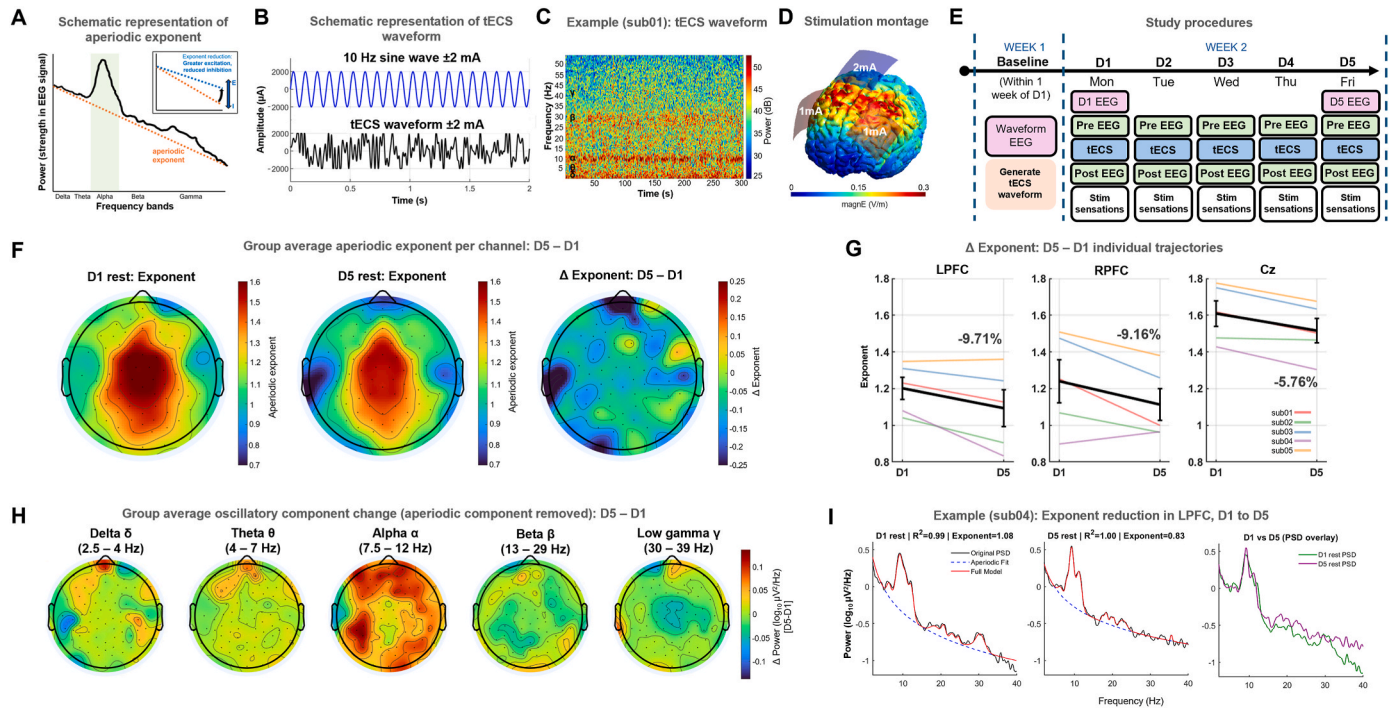


Fig. 1. tECS conceptualization, target identification and target engagement. (A) Schematic illustration of EEG aperiodic exponent, demonstrating the natural 1/f decay in the frequency spectrum. A reduced exponent is associated with a relative shift toward higher-frequency neural activity, consistent with a more excitation-dominated neural population profile (demonstrated by blue dashed line). (B) Comparison of 10 Hz (alpha) tACS sine wave (top) and an example trace of a tECS waveform (bottom) over a random 2 second sample; both at 2 mA (zero-to-peak). tECS waveforms, which contain steeper temporal transitions and broader frequency spectra compared to synthetically generated sine waves, are hypothesized to more effectively engage neuronal populations [3,12]. (C) Example time-frequency plot spectrogram (1–59 Hz) of five-minute stimulation waveform block in one participant (sub01), demonstrating natural frequency structure present in EEG. (D) SimNIBS [13] group-averaged E-field map in 5 mm ROI (|E|, V/m) for F3/F4 (+1 mA)/Cz (–2 mA) of $n = 5$ representative females from open source MRI data [14], 18–45 years, color bar scaled to top 99th percentile of whole brain E-field (V/m). (E) Study timeline demonstrating waveform EEG and D1, D5 outcome HD-EEGs (pink) as well as immediate pre-post stimulation EEG (green). (F) Group averaged topographic plot of aperiodic exponent per electrode, where orange/red indicates increased exponent (steeper), and turquoise/blue indicates decreased (flatter) exponent ($n = 5$). Left panel demonstrates D1 exponent topographic plot (see Fig. S7 for oscillatory components), middle panel demonstrates D5 exponent topographic plot, right panel demonstrates the change (D5–D1) topographic plot. (G) Observed decrease in aperiodic exponent in regions under stimulation electrodes between D1 and D5 shown by spaghetti plots of individual participant data ($n = 5$). Results were not statistically evaluated. (H) Group averaged topographic plot of D5–D1 change in oscillatory components (delta, theta, alpha, beta, low gamma frequency bands with aperiodic component removed using the MATLAB FOOOF [7] toolbox; 2–40 Hz, fixed aperiodic mode), presented as log power spectral density (PSD) values ($n = 5$). (I) Example of exponent reduction in one participant (sub04): D1 and D5 FOOOF fit highlighting original PSD, aperiodic fit, and full model for LPFC ROI (left and middle), as well as superimposed D1 and D5 full PSD model demonstrating reduction in aperiodic exponent at D5 vs. D1. LPFC, left prefrontal cortex; RPFC, right prefrontal cortex; Cz, central electrode cluster.

0.98). The five-minute waveform was duplicated into two sequential segments and stitched together, creating a 10-min waveform. A 20-s ramp-up and 3-s inter-segment ramps were used to avoid discontinuities and current spikes. The blocks (4×10 min, 2 mA zero-to-peak) were loaded into the neuroConn DC-Stimulator MC and verified with an oscilloscope (Supplementary Methods).

The results supported our hypotheses. tECS was safe (no serious adverse events), feasible (five enrolled within one month, 100 % retention), and tolerable (all sessions completed). Three “high” sensations were reported across 25 sessions (two “tingling”, one “pressure”) but did not affect tolerability (Table S4). Four of five participants showed a reduction in aperiodic exponent from D1–D5 across all stimulation regions (LPFC, RPFC, Cz) (Fig. 1F–G, 1I). The observations in our pilot sample ($n = 5$) are purely descriptive in nature, and no statistical evaluations or analyses were conducted. LPFC exponent decreased by -0.11 (SD 0.10; -9.71 %) and offset by -0.19 (SD 0.14, -26.16 %), with the largest changes in LPFC, the scalp location where the tECS waveform was derived from (Fig. 1G–S4; Table S5–S6). Similar changes appeared in RPFC, with smaller changes at Cz. Stimulation adjacent ROIs (frontal midline, central left, central right), demonstrated greater exponent reductions than stimulation regions (Fig. S5). Oscillatory PSD analyses with aperiodic component removed demonstrated mean LPFC alpha power increases of $0.14 \log_{10}(\mu V^2/\text{Hz})$, while other bands

remained largely unchanged (Fig. 1H; Fig. S8). PSD analyses including aperiodic component demonstrated decreased LPFC delta ($-0.17 \mu V^2/\text{Hz}$ [-10.18 % relative to D1]) and theta power (-0.06 [-7.18 %]) and increased alpha (0.11 [12.86 %]) and gamma power (0.01 [11.15 %]) (Fig. S8), consistent with the exponent reduction. Observations from Fig. S6 daily EEGs illustrate a progressive decrease in LPFC and RPFC exponent from D2 through D5, consistent with the overall D1 and D5 pattern; however, portions of the data were missing at specific time-points (3/50 recordings missing; see Fig. S6 caption).

tECS departs from conventional tACS paradigms by using endogenously derived waveforms that are systematically modified and re-applied exogenously through the scalp to perturb specific features of human neurophysiology. By integrating oscillatory and aperiodic EEG features, tECS may simultaneously act via rhythmic entrainment and broadband, non-entrainment network mechanisms. Preserving oscillatory components with added endogenous asymmetries (i.e., rapid, non-linear fluctuations) may better engage neuronal populations than sinusoids due to the sharp voltage transients, akin to sawtooth stimulation [12]. The irregular rise and fall of the waveform may also influence non-linear, non-oscillatory neural mechanisms to produce stochastic resonance-like dynamics, such as those elicited in transcranial random noise stimulation (tRNS) [15]. tECS differs conceptually from tRNS, as it represents a deterministic reconstruction of the participant’s own neural

activity, with highly similar phase structure and a structured power spectrum. Thus, tECS departs from synthetic stimulation patterns by using EEG-derived waveforms that retain naturalistic structure, with the rationale that these may elicit more effective neural engagement than synthetic stimulation paradigms.

Despite promising initial results, including safety, feasibility, tolerability, and preliminary neurophysiological target engagement, this was a small, open-label pilot study conducted in a non-generalizable population; therefore, effects of uncontrolled factors unrelated to stimulation cannot be fully excluded. Larger controlled studies across broader demographics are required to establish the specificity and reproducibility of tECS neurophysiological effects. Future studies in our team will examine how tECS can be applied to clinical populations, such as antenatal depression (Panda-tACS clinical trial: NCT06979154), providing a potential framework for targeted neuromodulation with biomimetic waveforms in psychiatric disorders.

In summary, tECS is a personalized, broadband stimulation method which uses naturalistic, endogenous stimulation waveforms intentionally modified to alter specific spectral properties, in this case, the aperiodic exponent, while retaining endogenous structure. Our pilot findings demonstrate safety, feasibility, tolerability, and descriptive observations of neurophysiological target engagement, positioning tECS as a potential next-generation approach in non-invasive neuromodulation.

CRediT authorship contribution statement

Athena Stein: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Ellen Floegel:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Mengsen Zhang:** Writing – review & editing, Software, Methodology. **Akshada Subramaniyan:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Swarup Sharma:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Zachary Feldman:** Writing – review & editing, Supervision, Methodology. **Michael Evers:** Writing – review & editing, Supervision, Methodology. **Julia Riddle:** Writing – review & editing, Supervision, Methodology. **Samantha Meltzer-Brody:** Writing – review & editing, Funding acquisition. **Flavio Frohlich:** Conceptualization, Methodology, Formal analysis, Software, Resources, Writing – original draft, Writing – review & editing, Supervision, Funding acquisition.

Ethics statement

This study was approved by the University of North Carolina at Chapel Hill Institutional Review Board and was conducted in accordance with the local legislation and institutional requirements. The participants provided written informed consent to participate in this study.

Data availability statement

Key data and analysis code supporting the findings of this study are available in an open-access repository at <https://osf.io/anpex/>

Disclosures

FF is a full-time employee of the University of North Carolina at Chapel Hill. FF is the lead inventor of IP issued to UNC and licensed to Electromedical Products International (EPI). In the last twelve months, FF has received consulting honoraria from the following entities: EPI and Insel Spital. FF is a shareholder of EPI. In the last twelve months, FF has received royalties from Academic Press and the University of North Carolina at Chapel Hill. JR is supported by the Foundation of Hope and

Sirtsei Pharmaceuticals. JR receives equity from, and is an advisory board member of, Cercle.AI. SMB has received grant funding from NIH and the Patient-Centered Outcomes Research Institute, as well research funding from Sage Therapeutics, Electromedical Products International, and Sirtsei Pharmaceuticals for clinical trials. SMB serves as a clinical advisor and professional corporation owner for Modern Health, a digital health company, and also serves as a scientific advisor to Seaport Therapeutics.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work the authors used ChatGPT in order to improve readability of originally drafted text. ChatGPT was not used to synthesize original content. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.brs.2026.103036>.

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Athena Stein^{a,b} , Ellen Floegel^{a,b}, Mengsen Zhang^{a,c},
Akshada Subramaniyan^{a,b}, Swarup Sharma^{a,b}, Zachary Feldman^{a,b},
Michael Evers^d, Julia Riddle^b, Samantha Meltzer-Brody^b,
Flavio Frohlich^{a,b,*} 

^a Carolina Center for Neurostimulation, Department of Psychiatry,
University of North Carolina at Chapel Hill, NC, USA

^b Department of Psychiatry, School of Medicine, University of North
Carolina at Chapel Hill, NC, USA

^c Department of Computational Mathematics, Science and Engineering,
Michigan State University, East Lansing, MI, 48824, USA

^d Department of Obstetrics & Gynecology, School of Medicine, University of
North Carolina at Chapel Hill, NC, USA

* Corresponding author. Carolina Center for Neurostimulation,
Department of Psychiatry, University of North Carolina at Chapel Hill,
NC, USA

E-mail address: flavio_frohlich@med.unc.edu (F. Frohlich).