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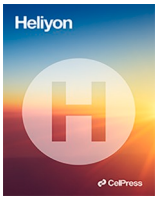

Research article

Exploring the synchronization of cortical networks via entrainment to intrinsic frequencies

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ABSTRACT

Introduction: Transcranial electrical stimulation (tES), including transcranial alternating current stimulation (tACS) and transcranial direct current stimulation (tDCS), is widely studied for its potential to modulate brain oscillations and connectivity, offering treatment options for neurological disorders like Alzheimer's, Parkinson's, and insomnia. In this study, we focus on investigating the efficacy of tACS and tDCS in entraining intrinsic cortical network oscillations through a computational model.

Materials and methods: We developed a 2D computational cortical neuron model with 2000 neurons (1600 pyramidal and 400 inhibitory), based on the Izhikevich neuron model. The network was structured to generate low-frequency oscillations, particularly within the delta (4 Hz) range. Both tACS and tDCS were simulated to assess their effect on network synchronization. An algorithm was employed to extract the network's intrinsic frequency and align stimulation frequencies accordingly.

Results: Our model successfully generated 4 Hz oscillations, characteristic of delta waves, associated with sleep states. t-ACS stimulation enhanced the power of the 4 Hz frequency, achieving effective synchronization with the intrinsic network dynamics. In contrast, tDCS failed to increase the power of 4 Hz oscillations and disrupted the excitatory-inhibitory balance of the network, reducing connectivity and synchronization. Our results demonstrate that tACS effectively enhances network synchronization and maintains excitatory-inhibitory balance by aligning with the network's intrinsic oscillatory frequency. In contrast, tDCS disrupts these dynamics, reducing connectivity and failing to entrain the target frequency. These findings suggest that tACS may hold greater potential for applications requiring precise network synchronization, while tDCS may have distinct but more limited efficacy in influencing oscillatory activity.

Conclusion: The study demonstrates the superior efficacy of tACS over tDCS in enhancing the synchronization of cortical networks by entraining intrinsic frequencies. Future research may extend this model by incorporating long-term plasticity mechanisms to better understand tES effects over longer time scales.

1. Introduction

Brain stimulation models are employed to either disorder pathological neuronal activity or enhance physiological processes, with the potential to bring significant therapeutic benefits. Neuropsychiatric disorders, including schizophrenia, Alzheimer's disease,

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Parkinson's diseases, psychiatric illnesses, cognitive impairments, and epilepsy, are increasingly recognized as network disorders characterized by dysfunctions in brain connectivity and communication [1]. These disorders are fundamentally linked to aberrant synchronization of neural activity, as well as the disorganization of cortical oscillatory rhythms [2,3]. The deficits in neural network connectivity are thought to underlie many of the cognitive and behavioral symptoms observed in these conditions [4]. Given these insights, there is a growing demand for advanced neuromodulation techniques that are grounded in a mechanistic understanding of these network disruptions. Despite the promise of brain stimulation technologies, such as transcranial alternating current stimulation (tACS) and transcranial direct current stimulation (tDCS), the development of paradigms that can selectively modulate neural oscillations across specific frequency bands has been hindered by a limited understanding of the underlying mechanisms. A deeper comprehension of how these stimulation techniques interact with brain networks is essential to advance their clinical applications and improve treatment outcomes for a range of neurological and psychiatric disorders.

Transcranial electric stimulation (tES) techniques, particularly non-invasive modalities such as tACS and tDCS, have shown promise in early trials for both cognitive enhancement and therapeutic interventions. Recent studies indicate their potential in treating neurological [5] and psychiatric conditions [6] and offer insights into how electrical stimulation interacts with complex networks of neurons [7,8]. These non-invasive techniques have garnered significant attention due to their ability to modulate brain activity safely and effectively. For example, early research on tACS has demonstrated frequency-specific effects on brain dynamics, which can be measured using electroencephalography (EEG) [9]. These effects have been linked to enhancements in memory retention, improvements in behavioral tasks [10], and therapeutic outcomes for sleep-related disorders [11], as well as improvements in motor and cognitive functions [12]. Neural oscillations, play a fundamental role in brain function, governing processes such as memory consolidation, attention, and sleep regulation. Techniques like tACS and tDCS offer non-invasive approaches to modulate these oscillations. tACS, in particular, induces frequency entrainment, a phenomenon where an external rhythmic stimulus aligns the frequency of neuronal oscillations with its own, enhancing synchronization between intrinsic and external signals [13]. This entrainment facilitates neural synchronization, or the coordinated timing of neuronal firing across the network, which underpins many cognitive and behavioral functions [14].

Despite these promising outcomes, the precise effects of tACS on large-scale cortical networks comprising millions of neurons remain poorly understood, particularly in relation to cognition and neuropsychiatric disorders. Small perturbations introduced by tACS to these networks can influence neural oscillations and connectivity, but the mechanisms underlying these changes remain inconclusive. This gap in knowledge presents a critical challenge for both the scientific community and clinical applications. Understanding how tACS influences network connections, neuronal oscillations, and their dynamic behavior across different cortical regions is essential for advancing its therapeutic potential. Addressing this challenge will not only contribute to a better understanding of brain function but also improve the efficacy of these interventions in treating neuropsychiatric disorders and enhancing cognitive abilities.

In this study, we employed a computational neuronal model to investigate the effects of weak perturbations on cortical network dynamics under the influence of tACS and tDCS. Our goal was to determine whether such low-intensity perturbations could effectively alter the microscopic behavior of the neuronal network during stimulation. To achieve this, we developed and utilized algorithms capable of detecting the network's intrinsic frequency, which was then used to guide the application of tACS. By matching the stimulation frequency and phase of the tACS to the network's intrinsic oscillatory patterns, we aimed to examine how closely synchronized stimulation could influence network behavior and dynamics. To ensure that our model aligns closely with established experimental findings, we configured its parameters based on experimental studies of cortical network dynamics, particularly those examining low-frequency oscillations and their underlying mechanisms. Specifically, our model simulates the interaction of excitatory and inhibitory neurons within a feedback loop structure, a configuration that experimental studies have shown to reliably generate low-frequency oscillations associated with delta-band activity. While constrained by computational simplifications, this approach provides a relevant framework for investigating transcranial electrical stimulation (tES) effects, allowing us to explore how tACS and tDCS may differentially influence network synchronization and excitatory-inhibitory (E/I) balance. Additionally, this approach was designed to deepen our mechanistic understanding of how electrical current perturbations interact with the complex dynamics of cortical networks. By simulating these interactions, we sought to explore how the modulation of network oscillations occurs in response to different stimulation parameters. Understanding these interactions is crucial for the development of more precise and targeted neuromodulation protocols. Through our simulations, we aim to contribute insights into designing safer and more efficient stimulation waveforms, potentially optimizing the therapeutic outcomes of tACS and tDCS while minimizing any adverse effects. This mechanistic knowledge could guide future experimental and clinical studies, improving the efficacy of brain stimulation techniques.

2. Materials and method

The computational model utilized in this study is based on the Izhikevich neuron model [15], which has been widely adopted for simulating the activity of cortical neurons due to its ability to capture both simple and complex neuronal dynamics with computational efficiency. The Izhikevich model was chosen for its balance between biological realism and computational efficiency, making it well-suited for large-scale simulations of cortical networks. Specifically, this model is able to capture essential neuronal behaviors that are crucial for simulating the effects of tES, including excitatory and inhibitory dynamics, network synchronization, and phase-locked oscillations. While alternative models such as the leaky integrate-and-fire model are computationally efficient, they do not exhibit the same level of dynamical complexity, particularly with respect to spiking and bursting patterns that are important for understanding neuronal responses to tES [15]. More complex biophysically detailed models, such as the Hodgkin-Huxley model, provide high physiological accuracy but are computationally intensive and less feasible for simulating large-scale neuronal networks (especially

when modeling the interactions between thousands of neurons, as in our study). In contrast, the Izhikevich model allows for efficient simulation of large networks while maintaining sufficient biological detail to study the effects of tACS and tDCS on network-level oscillations and synchronization. This balance of complexity and computational efficiency is particularly valuable for investigating how different tES protocols influence cortical network dynamics at the level of individual neurons and across large networks.

In our simulations, the model was configured to mimic the behavior of cortical neurons, particularly generating low-frequency oscillations characteristic of sleep-like states. We specifically modulated the neuronal network to replicate these low-frequency oscillations and implemented an algorithm designed to identify the intrinsic oscillatory patterns. Once the algorithm detected these patterns, we applied targeted stimulation to amplify the power of the corresponding frequency bands, thereby reinforcing the network's oscillatory behavior in a controlled manner. This approach allows for the enhancement of specific neuronal rhythms, offering insights into how modulating intrinsic frequencies can influence brain network dynamics.

The Izhikevich model was selected for its ability to realistically replicate the spiking dynamics observed in the cortical regions of the brain. The cortical computational model is constructed in a two-dimensional (2D) grid, comprising 2,000 neurons organized in a 4:1 ratio of pyramidal neurons (PY) to inhibitory neurons (IN). Specifically, the network includes 1,600 PY and 400 IN. The behavior of each neuron in the model is governed by a system of two coupled nonlinear ordinary differential equations, as described in the original Izhikevich framework [15]. This equation updating the membrane potential was following:

$$dv / dt = 0.04v^2 + 5v + 140 - u + I_{noise} + I_{syn} - G^{EX}\left(v - v^{AMPA}\right) - G^{IN}\left(v - v^{GABA}\right) \tag{1}$$

$$du / dt = u + a(bv - u) \tag{2}$$

with after spike reset

$$\text{If } v \geq 30 \text{ then } v \rightarrow c \tag{3}$$

and

$$u \rightarrow u + d \tag{4}$$

In the model, the variables v and u are dimensionless, where v represents the membrane potential of the neurons, and u is a membrane recovery variable. The variable u regulates the activation of the potassium (K^+) ionic current and the inactivation of the sodium (Na^+) ionic currents, providing negative feedback to v. The model uses four dimensionless parameters a, b, c, and d to describe the dynamics of neuronal activity. The parameter a determines the time scale of the recovery variable u and is set to 0.01 for PY, while it ranges from 0.01 to 0.09 for INneurons, introducing heterogeneity among the IN neurons. The parameter b reflects the sensitivity of the recovery variable u to changes in the membrane potential, with values set at 0.199 for PY neurons and ranging from 0.25 to 0.20 for IN neurons. The parameter c, which defines the reset value of the membrane potential v after a spike due to rapid high-threshold potassium conductance, is set between −50 and −65 for PY neurons and fixed at −65 for IN neurons. Finally, the parameter d, which controls the reset of the recovery variable u after a spike caused by slower high-threshold sodium and potassium conductance, is set between 8 and 2 for PY neurons and fixed at 2 for IN neurons. In our model, we employed regular spiking (RS) neurons for the PY neurons, as these represent the most common neuronal type found in the cortex, and fast spiking (FS) neurons for the IN neurons, following the Izhikevich neuron model [13]. To maintain the heterogeneity of the PY neurons, we introduced variability but biased the distribution towards RS cells. The membrane potential v is measured in millivolts (mV), and time t is measured in milliseconds (ms). To model synaptic interactions, we specified the reversal membrane potentials for the neurons for PY neurons, we used values corresponding to the amino hydroxy methyl isoxazole propionic acid (AMPA) receptors, while for IN neurons, we used values associated with gamma-aminobutyric acid (GABA) receptors. The reversal potentials were set at 0 mV for AMPA ($v^{AMPA} = 0$) and −80 mV for GABA ($v^{GABA} = -80$), respectively.

In our model, we incorporated two types of currents. The first is the synaptic current (I_{syn}), which is normally distributed across the PY neurons and scaled by a factor of 5, while for the IN neurons, it is scaled by a factor of 2 within the synaptic connections. These synaptic connections were structured to generate low-frequency oscillations and facilitate the transmission of conductance and presynaptic potentials between neurons. Additionally, the connections include an exponential decay component, which is applied to each neuron in the network. Synaptic conductance was updated dynamically to reflect the interactions between connected neurons. We update the synaptic conductance as

$$G^{EX'} = G^{EX} * e^{-\mathrm{d}t/\tau EX} \tag{5}$$

$$G^{IN'} = G^{IN} * e^{-\mathrm{d}t/\tau IN} \tag{6}$$

The total synaptic conductance for presynaptic neurons is represented by G^{EX} for PY neurons and G^{IN} for IN neurons. Their respective decay time constants, τEX for PY neurons and τIN for IN neurons, were set to 0.2 ms and 0.3 ms. The variable dt refers to the time elapsed since the most recent presynaptic potential. The synaptic connections for PY neurons are governed by short-term synaptic depression, represented by the variable 'd', which reflects the synaptic strength. A value of 1 corresponds to the absence of depression, indicating normal synaptic function, while a value of 0 indicates full synaptic depression.

$$G^{EX'} = d * G^{EX} \tag{7}$$

Recovery time variable set to 30 ms, denoted by τD. PY neuron connections updated dynamically based on presynaptic action potential of PY neurons

$$D = d^{*}r \tag{8}$$

The depression coefficient r is set to a constant value of 0.6. The connections between PY and IN neurons are randomly distributed, where each PY neuron is connected to 121 other PY neurons with a connection probability of 0.0006 ($G_{PY-PY} = 0.0006$). Additionally, each PY neuron forms synaptic connections with 29 IN neurons at a probability of 0.0002 ($G_{PY-IN} = 0.0002$). In turn, each IN neuron connects to 49 PY neurons to facilitate feedback propagation, with a connection probability of 0.0004 ($G_{IN-PY} = 0.0004$). Moreover, IN neurons also connect with other IN neurons.

To investigate network dynamics under stimulation, we employed algorithm to calculate intrinsic frequency, amplitude and phase spectra, and phase clustering. The intrinsic frequency of the network was determined by applying a Fast Fourier Transform (FFT) to the summed membrane potentials across all neurons over a 500 ms time window, yielding a power spectral density (PSD) plot in which the peak frequency represented the network's intrinsic oscillation. For amplitude and phase spectra calculation, we used the Hilbert transform on the summed signal to obtain instantaneous amplitude and phase values, allowing us to analyze the frequency-specific power and track phase stability across time. To visualize phase alignment, we generated a polar plot based on the phase data obtained at 4 Hz, the network's intrinsic frequency. In polar plot, each point represents the phase of the network at each time point, with clustering around a specific angle indicating phase-locking and stable synchronization. This phase clustering reflects the degree to which neuronal oscillations align over time, offering insight into the coherence and stability of network dynamics under tACS.

To ensure accurate modeling of transcranial stimulation, specific details on the amplitude, frequency, and waveform characteristics of tACS and tDCS inputs were incorporated into the simulations. For tACS, a sinusoidal waveform with a frequency of 4 Hz was used, aligned with the intrinsic oscillatory dynamics of the network. The amplitude of the tACS stimulation was set to 12 pA (pA) to simulate low-intensity current. In contrast, tDCS employed a direct current waveform with a constant amplitude of 12 pA (pA) to induce steady polarization effects on the network. Both stimulation protocols were applied to a subpopulation of excitatory neurons, representing localized stimulation regions, and the stimulation duration spanned to capture immediate entrainment effects. These parameters were selected to simulate realistic stimulation characteristics while maintaining computational feasibility.

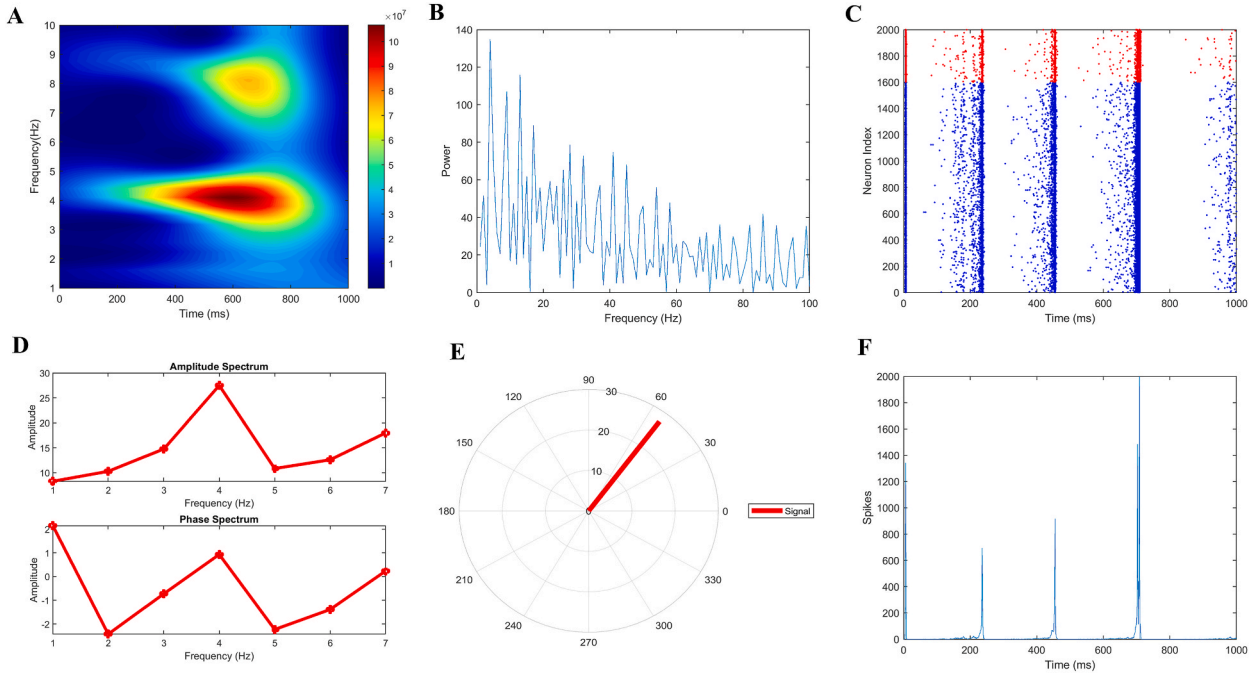

Fig. 1. Parameters of cortical computational model to generate a 4 Hz frequency with oscillatory activity. A: Spectrogram showing the temporal evolution of power across frequency bands, with a dominant peak at 4 Hz indicating baseline delta activity. B: Power spectral density (PSD) plot displaying frequency-specific power levels, highlighting the 4 Hz peak as the primary oscillation. C: Spike raster plot illustrating the firing patterns of pyramidal (PY) neurons (blue) and inhibitory (IN) neurons (red). Synchronized firing within 4 Hz oscillatory cycles is evident across the network. D: Phase spectrum plot showing amplitude and phase relationships, with a consistent phase angle at 4 Hz, supporting stable phase coherence. E: Polar plot representing the phase angle distribution at 4 Hz, with a clustering around 58° indicating phase-locking behavior in the network. F: Represents the spike along the time of neurons which increases as it forward along the time with spiking neurons.

3. Results

The objective of our model is to generate low-frequency oscillations within the cortical network, mimicking the diverse frequency patterns typically observed in the cortex [16]. By applying tDCS and tACS, we aim to achieve frequency entrainment, with the potential to develop therapeutic applications for conditions such as sleep disorders, relaxation, anxiety reduction, and depression. Our simulations are designed to capture the collective behavior of neurons, inducing lower frequency oscillations while applying low intensity tACS and tDCS to observe their effects on network dynamics.

We began by simulating our model, consisting of 1,600 PY neurons and 400 IN neurons, each with distinct synaptic connections. The time scale ($a = 0.01$) and sensitivity ($b = 0.199$) of the recovery variable were adjusted for RS excitatory neurons to promote slow recovery dynamics and initiate a saddle-node (Andronov-Hopf) bifurcation at the resting state [13]. This configuration led to the generation of low-frequency oscillations due to hyperpolarization, producing a 4 Hz rhythm (Fig. 1B). After tuning the model parameters, the spectrogram revealed dominant frequencies in the delta and theta bands, with peaks at 4 Hz and 8 Hz (Fig. 1A). The spike trains showed that neurons fired synchronously at regular intervals, and PY and IN neurons became synchronized across the entire network (Fig. 1C), further contributing to the generation of these frequencies. To analyze the network's oscillatory behavior, we computed the amplitude spectrum, which exhibited a prominent peak at 4 Hz, indicating that neuronal activity reached its maximum amplitude at this frequency. This finding suggests that the neurons' oscillatory behavior within the network is most pronounced at 4 Hz, which aligns with brain rhythms typically observed in the theta band (Fig. 1D). In addition to the amplitude analysis, we derived the phase spectrum to examine the phase relationships between different lower frequencies in the network. At 4 Hz, the phase spectrum showed a consistent phase angle, demonstrating the stability and coherence of the neurons' oscillatory activity at this frequency. The uniformity in the phase spectrum further supports the amplitude spectrum's findings, reinforcing the significance of 4 Hz as a key frequency in the network's dynamics (Fig. 1D). To explore the phase characteristics in more detail, we generated a polar plot to represent the phase angle distribution at 4 Hz. The plot revealed a concentrated clustering around 58°, indicating a strong phase preference at this angle. This suggests phase-locking behavior at 4 Hz, with the clustering at 58° reflecting a stable and synchronized oscillatory state within the network at this frequency (Fig. 1E). To ensure that our model aligns closely with established experimental findings, we configured its parameters based on experimental studies of cortical network dynamics, particularly those examining low-frequency oscillations and their underlying mechanisms. Specifically, our model simulates the interaction of excitatory and inhibitory neurons within a feedback loop structure, a configuration that experimental studies have shown to reliably generate low-frequency oscillations associated with delta-band activity. While constrained by computational simplifications, this approach provides a relevant framework for investigating tES effects, allowing us to explore how tACS and tDCS may differentially influence

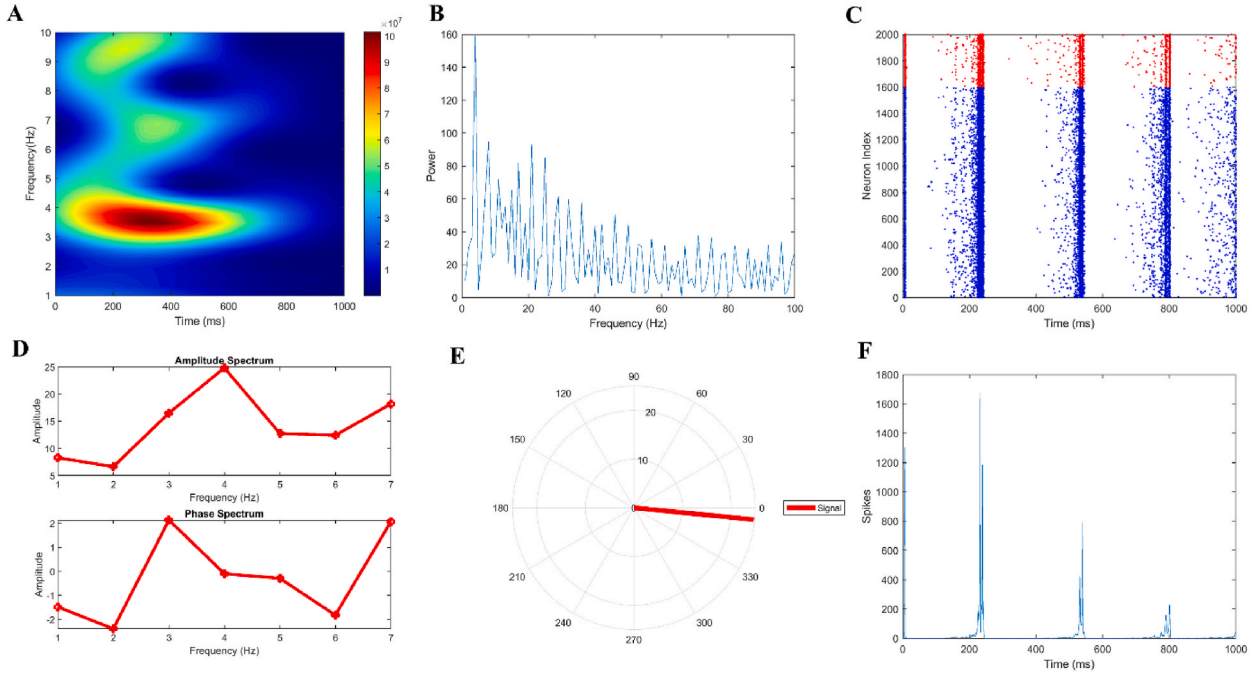

Fig. 2. Stimulation of cortical computational model with transcranial direct current (tDCS). A: Spectrogram after tDCS stimulation at 12 pA, showing minimal increase in 4 Hz power and a lack of frequency-specific entrainment. B: PSD plot illustrating that while power at 4 Hz shows a slight increase, it is not comparable to baseline synchronization. C: Spike raster plot depicting neuronal firing patterns, with reduced synchrony between PY (blue) and IN (red) neurons under tDCS stimulation. D: Phase spectrum plot after tDCS stimulation, showing a decrease in 4 Hz amplitude and a shift in the phase angle. E: Polar plot of the 4 Hz phase angle distribution under tDCS, with diffuse clustering indicating a lack of stable phase-locking. F: Spike activity map displaying reduced synchronized firing over time, suggesting diminished E/I balance.

network synchronization and excitatory-inhibitory (E/I) balance.

Our model's intrinsic 4 Hz oscillation emerges from the interplay between PY and IN neurons within a structured feedback loop, with synaptic parameters set to support low-frequency oscillatory activity. This E/I feedback loop operates through excitatory inputs from PY neurons to IN neurons, which in turn provide inhibitory control back onto PY neurons. The frequency of this oscillation is determined by the synaptic decay constants for excitatory (τEX) and inhibitory (τIN) connections, which were specifically tuned to produce delta-band oscillations. This synaptic interplay creates a rhythmic balance within the network, where excitatory activity drives oscillatory peaks and inhibitory feedback maintains stability, supporting synchronized 4 Hz activity across the network. This mechanism provides a basis for examining how external stimulation particularly tACS might enhance network coherence by aligning with these intrinsic oscillatory dynamics.

To further investigate the effectiveness of tDCS and tACS in the cortex, and determine which method better stimulates low-frequency oscillations for treating sleep-related disorders such as insomnia, we applied both tDCS and tACS to the model using the same amplitude of 12 pA. There is currently no clear evidence indicating which type of electrical stimulation tDCS or tACS best modulates theta or delta frequency ranges, which are important for the treatment of such disorders. Therefore, we first applied tDCS.

Our results showed that tDCS did not significantly enhance the power of the 4 Hz frequency (Fig. 2A), though there was a slight increase compared to the baseline model spectrum (Fig. 2B). Furthermore, the spike train analysis revealed that neuronal synchronization was maintained, with both PY and IN neurons firing in a synchronized manner, and without any disruption to the network's oscillatory behavior (Fig. 2C). Despite the synchronized firing, the amplitude spectrum indicated a slight decrease in amplitude at 4 Hz, suggesting that tDCS was unable to significantly induce this frequency (Fig. 2D). A similar observation was made in the phase spectrum, where the 4 Hz frequency did not align with the corresponding amplitude (Fig. 2D), and the phase angle shifted to 31°, which did not match the network's natural oscillatory activity (Fig. 2E). Looking at the spike behavior of individual neurons, we found that they spiked initially but later ceased to do so, likely because the stimulation failed to capture the network's maximum frequency response. This suggests that the network was unable to entrain to the 4 Hz frequency response early in the simulation (Fig. 2F). The implementation of tDCS stimulation is detailed in equation (9).

$$dv/dt = 0.04v^2 + 5v + 140 - u + I_{tDCS} + I_{syn} - G^{EX}(v - v^{AMPA}) - G^{IN}(v - v^{GABA}) \quad (9)$$

The results of the tDCS stimulation in our model did not meet expectations, as tDCS did not effectively modulate the frequency response or provide a therapeutic benefit, at least within the context of our computational model. To further investigate the impact of tACS, we applied the same current amplitude (12 pA) to observe whether it would produce a stronger stimulation effect on the network compared to tDCS. We implemented the tACS formula using a sine wave ($I_{tACS} = A*Sin(2*pi*f*t)$; where f is frequency and t is time),

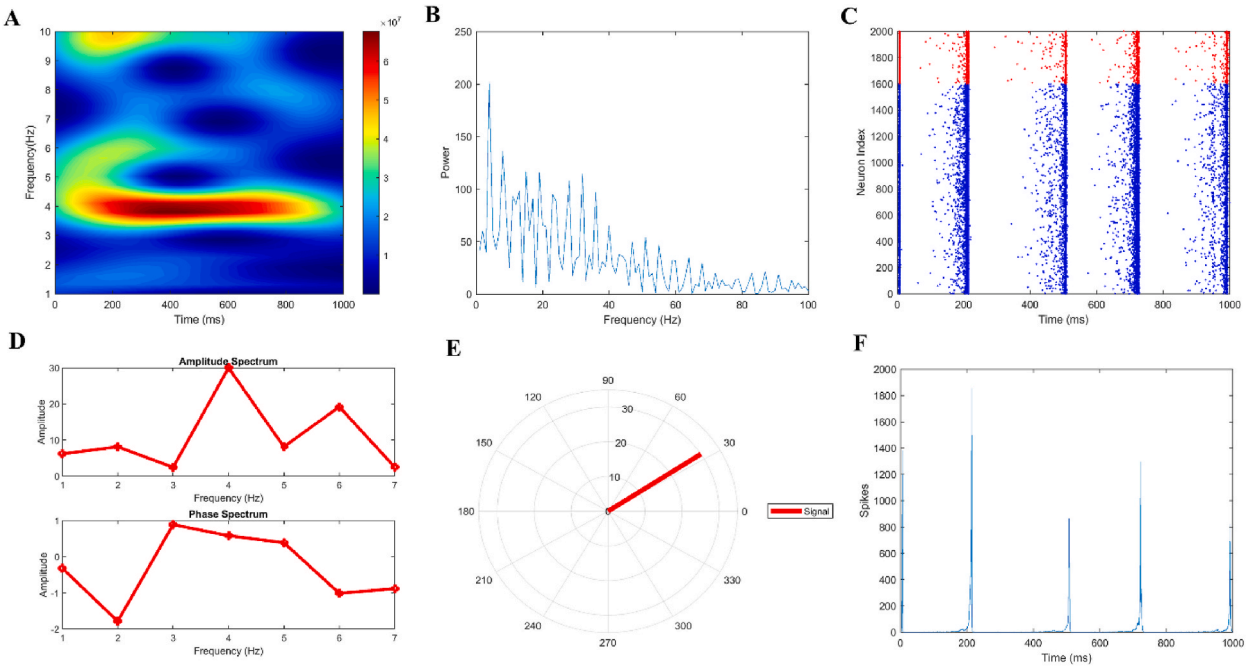

Fig. 3. Stimulation the cortical computational model with the 4Hz frequency with tACS. A: Spectrogram after 4 Hz tACS stimulation at 12 pA, showing sustained power increase at 4 Hz and effective frequency entrainment. B: PSD plot showing enhanced power at 4 Hz, reflecting successful entrainment of network oscillations. C: Spike raster plot with PY (blue) and IN (red) neurons, indicating synchronized firing across the network under tACS. D: Amplitude and phase spectrum showing a pronounced peak at 4 Hz with consistent phase alignment. E: Polar plot showing strong clustering around the target phase angle, indicative of stable phase-locking. F: Spike activity map showing sustained synchronous firing, demonstrating enhanced E/I balance with tACS.

selecting a 4 Hz frequency to synchronize with the network activity. In this case, no phase adjustment was applied for the t-ACS stimulation and used equation (10) for tACS stimulation.

$$dv/dt = 0.04v^2 + 5v + 140 - u + I_{tACS} + I_{syn} - G^{EX}(v - v^{AMPA}) - G^{IN}(v - v^{GABA}) \quad (10)$$

The impact of tACS on our model led to an increase in the power of the 4 Hz frequency. The spectrogram plot (Fig. 3A) shows a clear amplification of the 4 Hz frequency during the simulation in PSD plot (Fig. 3B), accompanied by more synchronized spike trains throughout the network (Fig. 3C). This indicates that the network entrained more effectively to its intrinsic frequency, maintaining synchronized activity without disrupting overall network dynamics (Fig. 3C).

Both PY and IN neurons fired in a coordinated manner, reflecting the network's synchronized oscillations. An analysis of the amplitude spectrum revealed that the 4 Hz frequency exhibited the highest amplitude, indicating the network's stability and coherence at this frequency (Fig. 3D). The phase spectrum further reinforced the importance of this frequency in the network's dynamics, showing that synchronization at 4 Hz began early in the stimulation (Fig. 3D). The phase remained stable for an extended period, although the phase angle shifted to 31° under tACS stimulation, suggesting a phase-locking behavior at 4 Hz. This phase adjustment contributed to a more synchronized and stable state within the network during the stimulation (Fig. 3E). Moreover, our computational model preserved the spiking activity of the network after tACS stimulation, in contrast to the tDCS model, where network spiking activity was not as prominent. This result suggests that tACS is more effective in enhancing and maintaining the spiking behavior of the network.

When comparing tDCS and tACS stimulation in the low-frequency cortical model, tACS exhibited a significantly higher degree of synchronization within the network, particularly when applied as a sine wave at the intrinsic frequency of the model. In contrast, tDCS primarily resulted in a direct increase in amplitude without achieving the same level of network entrainment. In contrast to the effects observed with tACS, tDCS does not induce frequency-specific entrainment at 4 Hz. Instead, the constant direct current stimulation applied by tDCS impacts the network's overall excitability, leading to a disruption in the E/I balance. This shift is evidenced by a reduction in synchronized firing across PY and IN neurons and a corresponding decrease in the power at 4 Hz. Upon applying tDCS, excitatory neurons (PY) might be exhibited a prolonged depolarization period, which led to a sustained increase in firing rates. This increased excitatory activity was not matched by a proportional rise in inhibitory neuron (IN) firing, resulting in an imbalance that disrupted coordinated oscillatory behavior. Specifically, the heightened excitatory activity reduced the efficacy of inhibitory feedback needed to maintain rhythmic 4 Hz oscillations, thereby diminishing network coherence. This E/I imbalance under tDCS contrasts with the effects of tACS, which periodically modulates excitability in sync with the target frequency, allowing for coherent oscillatory

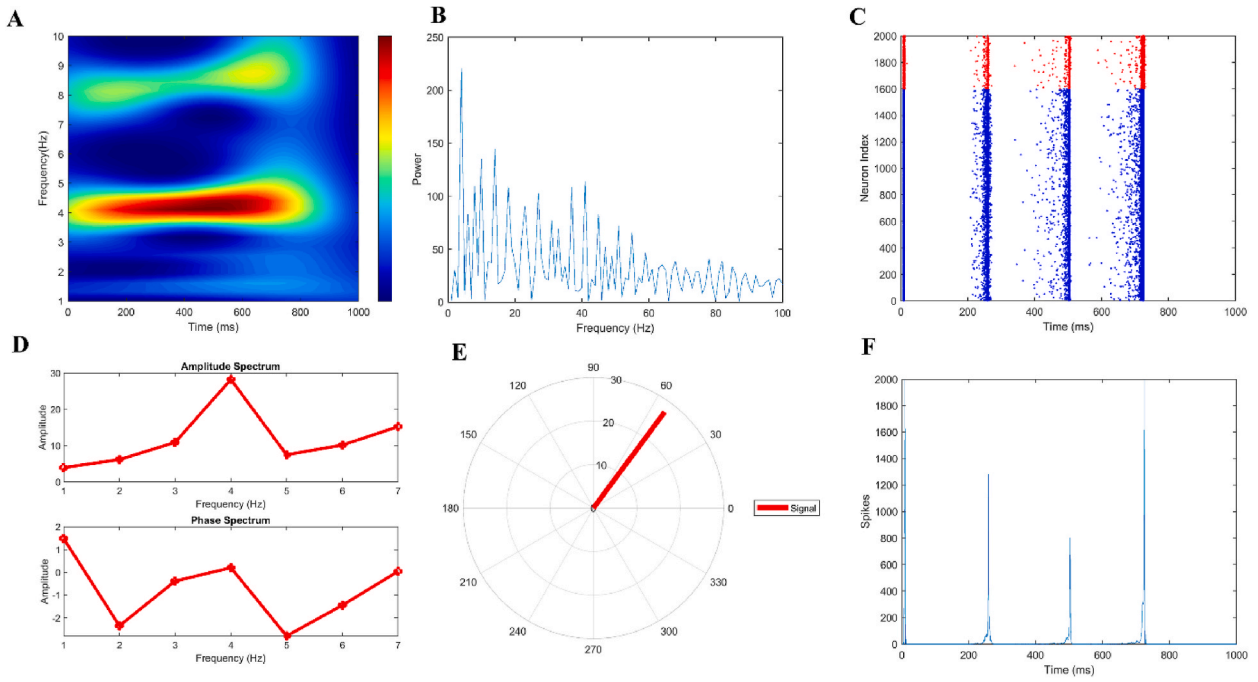

Fig. 4. Stimulation of t-ACS with algorithm in cortical computational model. A: Spectrogram showing the highest power concentration at 4 Hz after applying the algorithm-aligned tACS, indicating optimal entrainment. B: PSD plot confirming peak power at 4 Hz, reinforcing the effectiveness of frequency alignment with the intrinsic network oscillation. C: Activity map illustrating synchronized firing patterns of PY (blue) and IN (red) neurons, maintaining coherence through phase-aligned stimulation. D: Amplitude and phase spectrum showing 4 Hz as the dominant frequency with consistent phase alignment, resulting in stable network dynamics. E: Polar plot of phase distribution after stimulation, showing phase-locking with clustering at a target angle below 60°. F: Spike activity map showing high network synchronization, with enhanced firing coherence and E/I balance post-stimulation.

patterns to emerge across the network. By applying a continuous current, tDCS induces non-oscillatory changes in baseline excitability, which appears to destabilize network synchronization at 4 Hz. These findings suggest that tDCS's lack of frequency specificity may hinder its effectiveness in entraining oscillations at specific frequencies, particularly within the delta range. To enhance the synchronization effect of tACS, we developed an algorithm that monitors the intrinsic behavior of the model, extracting both the maximum frequency and its corresponding phase. This allowed us to apply tACS stimulation at the exact frequency required for optimal network entrainment.

Upon implementing this algorithm, tACS successfully generated a 4 Hz frequency, which closely matched the model's intrinsic frequency. The phase of the tACS signal was also aligned with the network's natural oscillations, ensuring effective stimulation (Fig. 4A). The PSD plot further confirmed the effectiveness of this approach, showing a peak at 4 Hz, indicating maximum power at this frequency (Fig. 4B). To evaluate whether the network remained synchronized after tACS stimulation, we analyzed the spike trains of both PY and IN neurons. The results (Fig. 4C) demonstrated that these neurons fired in synchrony, maintaining stable oscillatory behavior throughout the simulation. This suggests that the tACS stimulation effectively reinforced the natural dynamics of the network, without disrupting its inherent rhythm.

The amplitude and phase spectrum analysis (Fig. 4D) revealed that the 4 Hz frequency remained dominant, with the amplitude peaking at this frequency, further supporting the strong network entrainment. Additionally, a polar plot of the phase distribution (Fig. 4E) showed that the phase angles clustered below 60°, indicating phase-locking behavior at 4 Hz. This phase alignment suggests a stable and coherent oscillatory state in the network after tACS stimulation. Finally, the spike trains (Fig. 4F) showed that the neurons continued to fire in synchrony after the stimulation, further demonstrating that the network successfully entrained to the 4 Hz frequency and maintained this behavior.

We also analyzed the Phase Locking values (PLV) to check the induced entrainment effect in the computational model without stimulation, demonstrates moderate synchronization, with PLV distributed across the matrix ranging between 0.1 and 0.6 (Fig. 5A). This pattern reflects intrinsic oscillatory dynamics and network coherence in the absence of external modulation. Under tDCS, the PLV

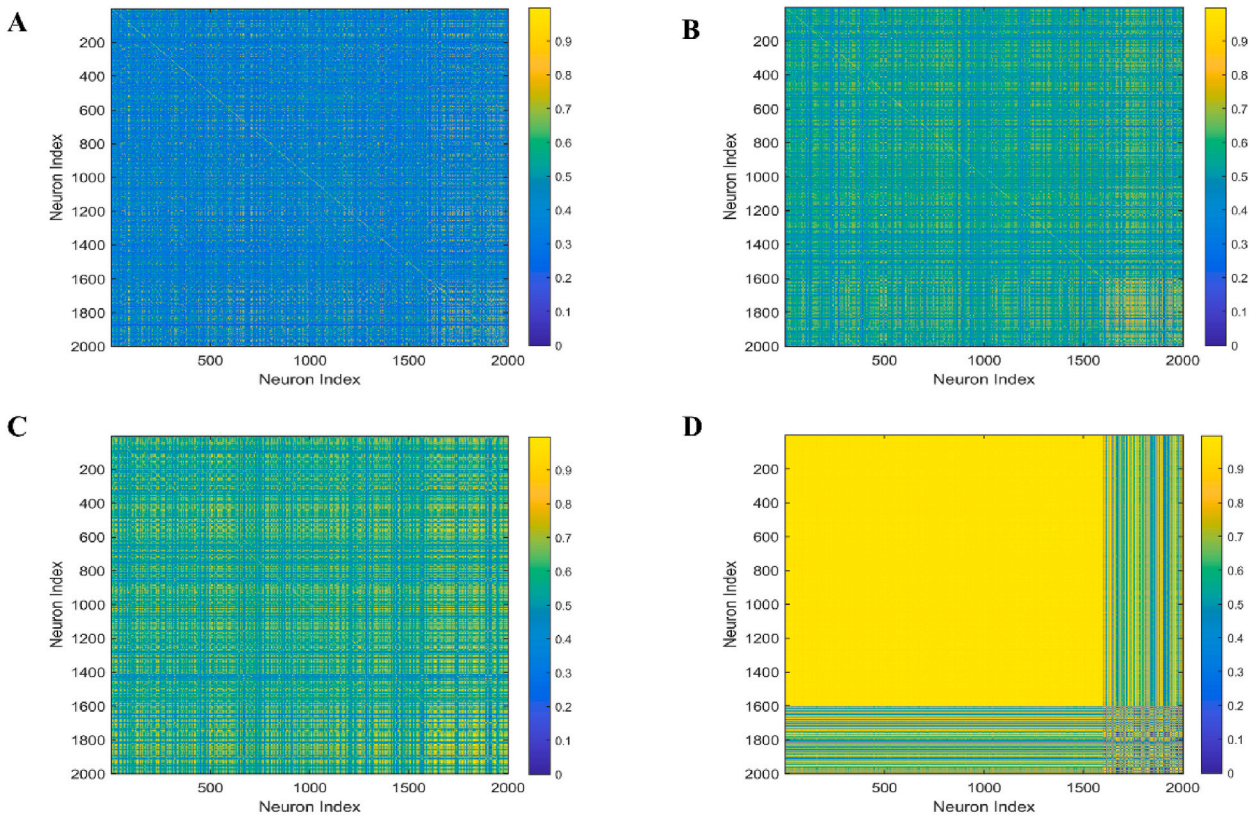

Fig. 5. Phase Locking Value (PLV) Matrices of Neuronal Synchronization Under Different Conditions. A, Baseline computational model: PLV matrix showing intrinsic oscillatory synchronization without external stimulation, with values distributed between 0.1 and 0.6. B. tDCS condition, PLV matrix under transcranial direct current stimulation, showing reduced synchronization compared to the baseline, with values primarily in the 0.1–0.4 range. C. tACS condition: PLV matrix under transcranial alternating current stimulation, showing enhanced synchronization, with values clustering around 0.6–0.9, indicating effective entrainment of intrinsic oscillations. D. Algorithm-enhanced tACS: PLV matrix demonstrating near-perfect synchronization, with values predominantly in the 0.9–1.0 range. This condition highlights the effectiveness of algorithm-guided stimulation in optimizing phase and amplitude for maximal network coherence. Color bars on the right of each matrix represent the PLV scale, where yellow indicates high synchronization and blue indicates low synchronization.

matrix shows a slight reduction in synchronization compared to the baseline, with the distribution concentrated around lower PLV values (0.1–0.4). This result indicates that tDCS disrupts network coherence and does not enhance intrinsic oscillatory synchronization in the delta frequency band. The application of tACS demonstrates a marked enhancement in synchronization, with PLV values clustering around 0.6–0.9. This increase aligns with the spectrogram results, where tACS induced a power increase in the 4 Hz delta band, emphasizing its role in synchronizing intrinsic low-frequency oscillations. The PLV matrix for algorithm-enhanced tACS exhibits the strongest synchronization, with PLV values predominantly in the range of 0.9–1.0. The high uniformity across the matrix highlights the effectiveness of the algorithm in optimizing the stimulation phase and amplitude, thereby achieving precise entrainment of neuronal oscillations.

The spectrogram analysis revealed that tACS induced a significant power enhancement in the 4 Hz delta band, while tDCS had minimal impact on power dynamics. The PLV matrices provide complementary insights, confirming that tACS enhances network synchronization, particularly when guided by the intrinsic frequency detection algorithm. Together, these findings highlight the differential effects of tACS and tDCS on network dynamics and the critical role of phase-aligned stimulation in maximizing synchronization.

4. Discussion

tES, including tACS and tDCS, is widely used in neuroscience research to modulate neuronal oscillations and improve brain connectivity. This non-invasive technique is applied to treat neurodegenerative conditions such as Alzheimer's disease [5], Parkinson's disease [17], and insomnia [18]. Electrical modulation works by altering neuron firing rates, either synchronizing or desynchronizing brain waves, which promotes new neuronal connections and enhances brain function [19]. In Parkinson's disease, tES has been shown to alleviate motor symptoms like tremors and rigidity by stimulating specific brain regions [17]. Additionally, tACS and tDCS have shown potential in improving cognitive function in Alzheimer's patients [5] and addressing sleep disorders such as insomnia by modulating brain activity [18]. Computational models of cortical neuron networks provide insights into how tACS and tDCS influence cortical oscillations. Algorithms that identify intrinsic frequency characteristics may improve the precision of network entrainment. This study examines the effects of tACS and tDCS on cortical networks, highlighting their potential to enhance neural modulation in vivo.

Building on foundational studies by Reato et al. [20] and Ali et al. [21], which explored tACS-induced network synchronization and the impact of tES on synaptic plasticity, our study delves into the network's intrinsic low-frequency oscillatory behavior. We highlight that tACS, in contrast to tDCS, naturally aligns with and enhances these oscillations within the 4 Hz delta band, a frequency range with important implications for cognitive and therapeutic applications, particularly in sleep modulation. Herrmann et al. [13] provided an extensive mechanisms underlying tACS and described general entrainment phenomena; our study builds on this by adding a computational perspective that specifically examines low-frequency cortical dynamics and the unique effects of tACS on the E/I balance at 4 Hz. By synchronizing stimulation phase and amplitude with the network's intrinsic oscillations, our model provides a detailed analysis of how tACS could potentially enhance network coherence and connectivity within the delta frequency. Further, Zhao et al. [22] investigated recent advancements in tACS models and brain oscillation dynamics. Our findings contribute to this field by demonstrating how intrinsic frequency detection algorithms can refine stimulation targeting and augment entrainment precision, offering a pathway for optimizing tACS applications in clinical contexts, such as treatments for sleep and neuropsychiatric disorders.

We developed a computational model of the cortical neuron network with 2000 neurons (1600 PY and 400 IN) using the Izhikevich neuron model. Parameters were adjusted, and connections established between PY and IN neurons to induce oscillations generating low frequencies, along with alpha, beta, and gamma frequencies. The model predominantly produces a 4 Hz frequency, corresponding to the N1 sleep stage and delta wave range, associated with early sleep [23], relevant for enhancing sleep quality [24]. The model shows maximum power at 4 Hz (Fig. 1B), with synchronized PY and IN neuron activity. Our results suggest tACS enhances 4 Hz power, aligning neuronal dynamics with stimulation frequency, potentially improving memory and cognition, consistent with Polanía, Nitsche [25]'s findings.

While our study primarily focused on slow cortical rhythms, it demonstrates that tACS enhances endogenous oscillations in our simulations by modulating network dynamics and influencing initiation sites. These initiation sites rapidly propagate laterally through local excitatory connections, facilitating network synchronization. In several regions of the network, the system operated near the threshold for substantial positive feedback via PY-PY coupling, which tACS stimulation pushed beyond the threshold, allowing these regions to become fully active initiation sites. This threshold behavior and nonlinearity are commonly observed in oscillatory neural networks, where periods of inactivity alternate with bursts of neural firing, as seen in cortical slow oscillations. The network dynamics identified in this study may be generalizable to other configurations of neural networks and different endogenous oscillations under tACS and tDCS stimulation, especially when combined with algorithmic approaches to track intrinsic frequencies. Additionally, our model exhibited sensitivity to weak perturbations, enabling the entrainment of intrinsic oscillations by tACS. This finding highlights the ability of tACS to interact with endogenous rhythms, further promoting the synchronization and enhancement of specific neural oscillations within the network.

The PLV analysis offers critical insights into the mechanisms underlying neuronal synchronization under different stimulation protocols. The baseline model demonstrates moderate synchronization, reflecting intrinsic oscillatory dynamics that form the foundation for external modulation. The disruption of network coherence under tDCS aligns with previous studies, which suggest that direct current stimulation modulates resting membrane potentials but lacks the phase-specific alignment necessary for enhancing oscillatory synchronization [21]. In contrast, tACS effectively aligns with and amplifies intrinsic oscillations, as evidenced by the enhanced PLV values. These results corroborate findings from Herrmann et al. [13], who reported that alternating current stimulation

is uniquely suited for entraining cortical oscillations due to its periodic nature. The observed enhancement in the delta band further supports the clinical relevance of tACS in modulating sleep-related oscillations and cognitive processes.

The algorithm-enhanced tACS condition represents a significant advancement in stimulation protocols. By aligning the stimulation phase and amplitude with intrinsic network dynamics, the algorithm achieved near-perfect synchronization, as indicated by the high PLV values. This precision highlights the potential for algorithm-guided stimulation to optimize therapeutic outcomes by targeting specific frequency bands and enhancing network coherence. The combined spectrogram and PLV results underscore the importance of frequency-specific and phase-aligned stimulation in achieving effective neuromodulation. While tDCS offers broader modulation of excitability, its lack of synchronization capabilities limits its efficacy in enhancing low-frequency oscillations. In contrast, tACS, particularly when optimized by intrinsic frequency detection algorithms, demonstrates robust synchronization effects, offering a promising pathway for therapeutic applications in sleep disorders, cognitive enhancement, and neuropsychiatric conditions. Future studies should explore the long-term effects of algorithm-enhanced tACS on plasticity and behavioral outcomes, as well as its applicability across different frequency bands and clinical populations.

Our findings on the efficacy of tACS in enhancing delta-band synchronization align with existing empirical research on the effects of tACS in biological systems. Several studies have demonstrated that low frequency tACS can effectively entrain delta oscillations, particularly in contexts related to sleep and cognitive processing. For instance, Helfrich et al. [26] observed that tACS applied in the alpha frequency range (approximately 10 Hz) enhanced alpha-band power in human participants, supporting our model's prediction that tACS can entrain neural networks at alpha frequencies. Moreover, studies such as those by Ketz et al. [27] found that delta-frequency tACS increased phase coherence and improved memory consolidation during sleep a process closely associated with delta oscillations. This empirical evidence aligns with our findings that tACS, when tuned to the intrinsic 4 Hz frequency, enhances network synchronization and phase coherence. These biological effects support the model's representation of delta-range entrainment as a feasible mechanism for enhancing network coherence in physiological settings. In contrast, the observed disruptive effects of tDCS in our model are also consistent with empirical data indicating that tDCS does not produce frequency-specific entrainment. Experimental studies, including those by Marshall et al. [28], have shown that while tDCS can modulate general excitability, it lacks the rhythmic specificity required for enhancing specific oscillatory frequencies like delta. Our model's results echo these findings, suggesting that tDCS may alter baseline excitability without providing the frequency-specific effects required for targeted delta-band synchronization. This comparison between our model and empirical findings provides support for the predictive value of our approach. By simulating tACS and tDCS effects on delta oscillations, our model offers insights into how these stimulation types may influence neural dynamics, with implications for future applications in enhancing sleep quality or cognitive performance. However, further empirical studies are necessary to validate and refine the model's applicability across diverse biological contexts. Our results highlight the superior efficacy of tACS compared to tDCS in achieving instantaneous entrainment of endogenous cortical oscillations, particularly when aligned with algorithm-driven synchronization of network dynamics. In contrast, tDCS stimulation in our model did not increase the power of any frequency band; instead, it reduced the effects and altered the baseline excitability of neurons. This change in excitability disrupted the connectivity between neurons, thereby inhibiting effective oscillations and diminishing the power of the 4 Hz frequency, as well as other frequency bands. Additionally, the phase relationship was negatively affected, interfering with the 4 Hz oscillation. We observed that overall network activity was reduced, with spike trains showing decreased firing synchronization, likely due to a mismatch in phase and a loss of E/I balance [29]. The PY-PY network activity was notably altered following tDCS stimulation, leading to weakened neuronal connections and disrupted oscillatory patterns. Previous studies, such as Miller et al. [30] and Keeser et al. [31], provide evidence that tDCS can modulate cortical oscillatory activity, primarily by shifting neuronal excitability rather than directly entraining oscillations. Our findings are consistent with this, showing that tDCS has limited efficacy in enhancing low-frequency synchronization compared to tACS. While tDCS may indirectly influence oscillatory dynamics through its effects on long-term synaptic plasticity, its lack of direct phase alignment with intrinsic oscillations constrains its immediate impact on network-level coherence, particularly in the 4 Hz delta band examined here.

A key limitation of our computational model lies in its focus on short-term network synchronization and low-frequency oscillations, which does not fully capture the broader spectrum of tDCS effects. For example, tDCS is known to induce changes in cortical excitability that persist beyond the stimulation period, potentially influencing higher-order cognitive functions over extended timescales. Our model does not incorporate long-term plasticity mechanisms, such as changes in synaptic strength, which are crucial for understanding the enduring effects of tDCS on neural networks. Additionally, the simplified structure of the model, which prioritizes computational efficiency, may not fully represent the complexity of large-scale brain dynamics or interactions with other oscillatory bands. Future studies should aim to integrate these features to provide a more comprehensive understanding of tDCS-induced effects.

While our computational model provides valuable insights into the mechanisms underlying tACS- and tDCS-induced oscillatory dynamics, it is important to acknowledge certain limitations. One key limitation lies in the restricted parameter testing performed in the current study. Although the model incorporates a realistic E/I balance and intrinsic low-frequency oscillatory dynamics, the parameter space explored such as synaptic strengths, intrinsic oscillatory frequencies, and stimulation amplitudes was limited. Broader exploration of these parameters could provide a more comprehensive understanding of how variations in neural and stimulation parameters affect network responses and entrainment across different frequency bands.

Additionally, our model's findings have not yet been validated in physiological neuronal networks or animal models. While the results align with theoretical and experimental studies, such as those by Miller et al. [30] and Keeser et al. [31], direct validation of the predicted effects of tACS and tDCS on oscillatory dynamics is necessary to establish their physiological relevance. Specifically, experimental studies in animal models or ex vivo preparations could help verify the observed modulation of delta-band oscillations and the unique effects on network synchrony and E/I balance.

Future work should address these limitations by expanding the parameter space explored in simulations to include more diverse

neural populations, varying connectivity patterns, and broader ranges of stimulation protocols. Such studies could reveal critical thresholds and dependencies that govern the efficacy of tACS and tDCS in enhancing or suppressing specific neural oscillations. Moreover, integrating experimental data from animal models or in vivo studies into the modeling framework would provide a more robust validation of the model's predictions. These studies would also facilitate the refinement of stimulation protocols for potential clinical applications, such as optimizing the dosing and targeting of tACS and tDCS for treating sleep disorders, cognitive dysfunctions, and neuropsychiatric conditions. Enhancing delta activity through tACS may improve sleep quality and benefit individuals with sleep disorders or age-related disruptions [28]. In cognitive enhancement, delta oscillations play a role in memory retention and the integration of information during slow-wave sleep (SWS). Studies, such as Ketz et al. [27], have shown that low frequency tACS during SWS enhances memory consolidation, aligning with our model's demonstration of successful 4 Hz network entrainment. This makes tACS a promising tool for supporting memory and learning in both healthy individuals and those with neurodegenerative disorders. Enhanced delta synchronization may also benefit neuropsychiatric conditions, such as major depressive disorder and schizophrenia, which are characterized by disrupted neural rhythms. Preliminary evidence suggests that tES can improve mood and cognitive function [32], and our findings provide a mechanistic basis for targeting delta-band oscillations with tACS as a potential neuromodulation strategy in these contexts. Our investigation demonstrates the superior efficacy of tACS compared to tDCS in achieving rapid entrainment of endogenous cortical oscillations. This was further supported by the algorithm, which successfully synchronized the network to the maximum power frequency while maintaining phase alignment. Nonetheless, our present model lacks the inclusion of long-term potentiation and other plasticity mechanisms over extended temporal scales while effective in simulating short-term network responses to tES, does not include long-term plasticity mechanisms, such as synaptic potentiation or depression. This limitation may impact the interpretation of our results in several ways, particularly regarding the sustained effects of tACS and tDCS. In real biological systems, long-term plasticity mechanisms are crucial for lasting changes in synaptic strength and network connectivity, which underlie memory consolidation, learning, and adaptive responses to repeated stimulation. Studies have shown that long-term potentiation (LTP) and long-term depression (LTD) contribute significantly to the efficacy of repeated or prolonged tES sessions, potentially enhancing or diminishing the effects of tACS and tDCS over time. For instance, research by Reis et al. [33] and Fritsch et al. [34] suggests that tDCS can induce synaptic changes that outlast the immediate stimulation period, highlighting the importance of plasticity for long-term modulation of cortical networks. In our model, the absence of long-term plasticity means that any effects observed under tACS or tDCS are limited to short-term network dynamics and do not reflect the cumulative effects of plastic changes that may occur with repeated or extended stimulation. Consequently, while our findings indicate that tACS can enhance synchronization and tDCS disrupts E/I balance in the short term, the lack of plasticity mechanisms limits our ability to predict how these effects would evolve with sustained or repetitive tES. The incorporation of plasticity mechanisms, such as Hebbian learning rules or spike-timing-dependent plasticity (STDP), in future models would enable more comprehensive simulations that capture the full scope of tES effects, including potential reinforcement or attenuation of network synchronization over time. Thus, while our model provides insights into the initial impact of tES on network oscillations, future studies incorporating long-term plasticity would be essential for understanding how these stimulation techniques might produce lasting therapeutic effects, especially in clinical applications targeting memory, learning, and long-term cognitive enhancement.

We have sought to provide a balanced perspective on the potential uses of tDCS and tACS. While tACS demonstrated superior performance in synchronizing low-frequency oscillations in our simulations, this does not diminish the value of tDCS in clinical contexts where direct modulation of neuronal excitability is advantageous. For instance, tDCS may be better suited for applications targeting long-term behavioral or cognitive changes, such as rehabilitation after stroke or treatment of mood disorders. In contrast, tACS appears more effective for tasks requiring precise modulation of rhythmic activity, such as enhancing slow-wave oscillations for improving sleep quality or cognitive enhancement. By aligning the choice of stimulation technique with specific therapeutic goals, clinicians can leverage the unique strengths of each method to optimize outcomes.

In summary, while our model highlights the advantages of tACS in entraining delta oscillations and improving network synchronization, it underscores the need for further research to elucidate the broader implications of tDCS and its role in long-term neural plasticity. A complementary approach, combining the strengths of both techniques, may offer a powerful strategy for addressing diverse neurological and psychiatric disorders.

In the context of computational modeling, the scaling of stimulation parameters amplitude, frequency, and waveform requires careful consideration to balance physiological relevance with numerical stability. In this study, tACS and tDCS were modeled with simplified yet representative parameters to facilitate the analysis of their effects on intrinsic network oscillations. While the chosen stimulation amplitudes and waveforms align with those used in experimental studies, it is important to acknowledge that the scaling of these inputs may not fully capture the complexities of in vivo neuromodulation. Future adjustments to stimulation parameters could enhance the model's physiological and clinical relevance. For instance, incorporating variability in tACS frequencies to reflect individual differences in intrinsic oscillatory patterns or exploring a wider range of tDCS amplitudes to simulate stronger polarization effects could provide deeper insights into the mechanisms of action. Additionally, adopting dynamic waveforms that mimic physiological rhythms may improve the model's predictive power for clinical applications. Scaling studies that systematically test these variations within the model, followed by experimental validation in physiological and clinical contexts, are crucial steps to bridge the gap between computational predictions and real-world outcomes. By refining the parameterization of tACS and tDCS inputs and integrating findings from in vivo studies, future research can improve the translational potential of computational neuromodulation models, ultimately advancing therapeutic applications in neurology and psychiatry.

5. Conclusion

In conclusion, this study demonstrates that 4 Hz tACS effectively enhances synchronization within cortical networks by entraining intrinsic low-frequency oscillations, while tDCS shows limited efficacy in this regard due to its non-rhythmic nature. Our findings provide mechanistic insights into the distinct effects of tACS and tDCS on network dynamics, highlighting the potential of tACS for therapeutic applications in sleep modulation, cognitive enhancement, and neuropsychiatric disorders. However, the study is constrained by a simplified model and the absence of long-term plasticity mechanisms, which limits its scope in capturing the broader impacts of transcranial electrical stimulation. Future research should incorporate more complex network models, expanded parameter testing, and validation through physiological and in vivo studies to refine these insights and enhance their translational relevance. This work establishes a strong foundation for optimizing stimulation protocols and advancing the clinical utility of neuromodulation techniques.

CRediT authorship contribution statement

Sandeep Kumar Agnihotri: Writing – review & editing, Writing – original draft, Software, Methodology, Investigation, Formal analysis, Conceptualization. **Jiang Cai:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Zhen Wang:** Writing – review & editing, Software, Project administration, Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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