Assessment of Transcranial Electrical Stimulation Effects on Brain Rhythms Measured by Invasive Electroencephalography

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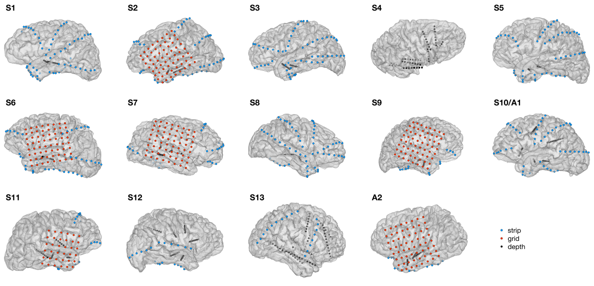
Introduction

- Transcranial electrical stimulation (TES) methods have been explored in over 70 different neuropsychiatric conditions.
- Transcranial alternating current stimulation (TACS) is a form of TES which delivers electrical current with a sinusoidal waveform of alternating polarities and potentially modulates oscillations important to cognition and disease.
- Low frequency TACS has been applied during NREM in healthy subjects to boost declarative memory, presumably by entraining slow-spindle oscillations. These stimulation parameters applied during waking rest have also been reported to result in widespread theta increases and improved encoding.
- The weakly positive and controversial behavioral effects of TACS underscore a lack of basic understanding of how applied electric fields acutely interact with ongoing brain activity.
- **Here we assess with intracranial recordings in humans whether low-frequency TACS (applied at commonly used stimulation frequencies, montages, and intensities) can acutely entrain spindle and gamma activity during NREM sleep, or theta activity during waking rest.**

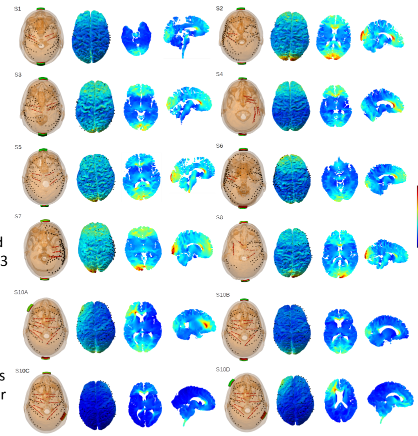
Methods

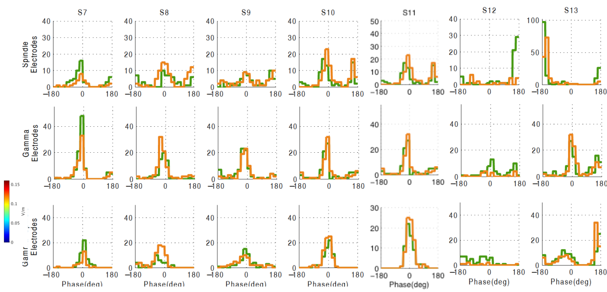
- Thirteen (N=13) subjects undergoing epilepsy surgery at a single center were included. Seven (7) subjects received TACS (0.75 Hz and 1 Hz) during NREM sleep (S7-13) and six (6) subjects received TACS during waking rest (S1-6).
- Stimulation intensities varied from 0.5-2 mA, limited by patient sensation and amplifier saturation.
- The TACS waveform recorded during iEEG was used to measure voltages at each electrode location and derive the electric fields between neighboring electrodes. A calibrated computational model was used to estimate field magnitudes in regions without electrode coverage.
- iEEG data was analyzed offline after subtraction of the TACS stimulation artifact.
- For sleep iEEG during TACS, segments were analyzed for phase-amplitude coupling (PAC) between high frequency oscillations (spindle, gamma) and phase of the low frequency activity (SO, spindle)
    - ➢ To measure entrainment to TACS, we measured power of spindle activity (14 Hz, 7 Hz bandpass) to phase of the TACS stimulation artifact (0.75, 1 Hz).
    - ➢ To measure entrainment during endogenous sleep (2 nights per subject) we measured power of spindle activity to the phase of the endogenous slow oscillation (SO). As secondary analyses, we also measured gamma (70-110 Hz)-SO and gamma-spindle PAC.
- For wake iEEG during TACS, segments were analyzed for PAC between theta activity (7 Hz bandpass, 3.5 bandwidth) and phase of the TACS waveform (0.75 Hz, 1 Hz). Secondary measures were alpha (10 Hz) and gamma modulation by TACS.
- As a control, 2 epilepsy patients (A1-2) were given 0.75 and 1 Hz acoustic stimulation during NREM sleep.



Results

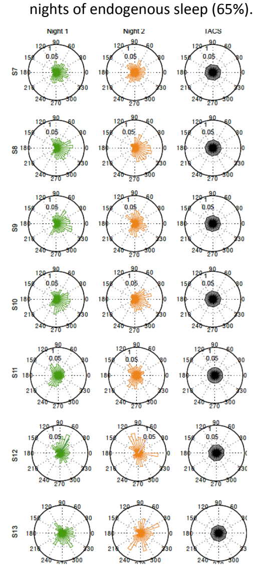
- We recorded from a total of 1700 electrodes in 13 subjects.
- After data cleaning, there were 695 electrodes analyzed during TES applied in wakefulness and 607 electrodes analyzed with TES applied in sleep.
- Electric fields reached maximal values of 0.43 V/m at the cortical surface for 2mA of stimulation.
- Efs were maximal under the electrodes and in deep structures such as periventricular WM.





- Mean preferred phase for all electrodes of of spindle (14 Hz) and gamma (70-110 Hz) activity to the up-phase of the SO.
- Low frequency TACS (0.75 and 1 Hz, <2 mA) did not modulate neural oscillations (theta, alpha, gamma) during wakeful rest.

- Spindle activity had a preferred phase to native SO. Spindle activity did not have a preferred phase to the phase of the TACS waveform (0.75 Hz, 1 Hz).
- One out of 607 electrodes demonstrated spindle entrainment during TES. In contrast, 484 out of 745 electrodes demonstrated spindle entrainment across 2 nights of endogenous sleep (65%).



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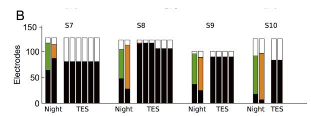

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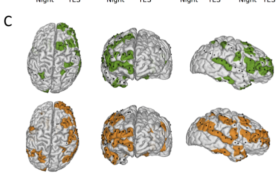

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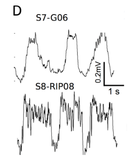
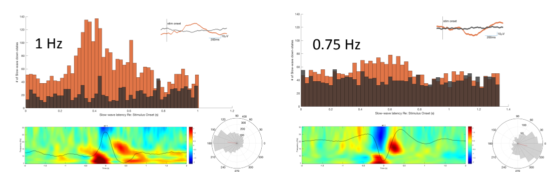


(A) Spindle power (14 Hz) relative to phase of endogenous SO (green and orange) and phase of TACS waveform (black). Both nights 1 & 2 have a similar preferred phase, but there is no preferred phase to the TACS waveform. (B) Fraction of recording electrodes which demonstrate significant PAC during endogenous sleep vs TACS.

C) Locations of electrodes with significantly entrained spindle activity for S8 during Night 1 (green, top row), and Night 2 (orange, bottom row). (D) Examples of spindle activity seen with the up-phase of the SO as seen in the raw EEG tracing of 2 subjects (in representative electrodes)

- Acoustic (red) vs. Sham (black) stimulation at 1Hz (left; A1 depth electrodes only) and 0.75Hz (right; A2 grid electrodes only) able to entrain slow-spindle oscillations.
- Slow-wave/Spindle PAC (bottom) confirms entrainment of sleep-related oscillations.



Conclusions

- This is the first human study to assess the direct physiological effects of TACS by measuring neural oscillations through invasive electroencephalography (iEEG).
- We found that low frequency TACS (0.75, 1 Hz) applied at commonly used stimulation intensities does not reliably entrain spindle activity during NREM sleep.
- In contrast, spindle and gamma activity were strongly entrained to SO activity in almost 2/3 of the electrodes in the depth and cortical surface electrodes across 2 nights of NREM sleep in all 7 subjects.
- Low frequency TACS (0.75 Hz, 1 Hz) applied during waking rest did not modulate theta, gamma, or alpha activity.
- Absence of entrainment with TACS likely results in part from the weak electric fields reaching the cortical surface (0.43 V/m for 2 mA).
- These findings suggest that higher intensity stimulation may be required to exert an instantaneous effect on network-level neuronal activity. However, applied current intensity is limited by safety, tolerability, and experimental conditions (i.e. sleep).
- Other modalities of neurostimulation, i.e acoustic, should be explored as alternative methods of modulating brain rhythms relevant to cognition and disease.

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