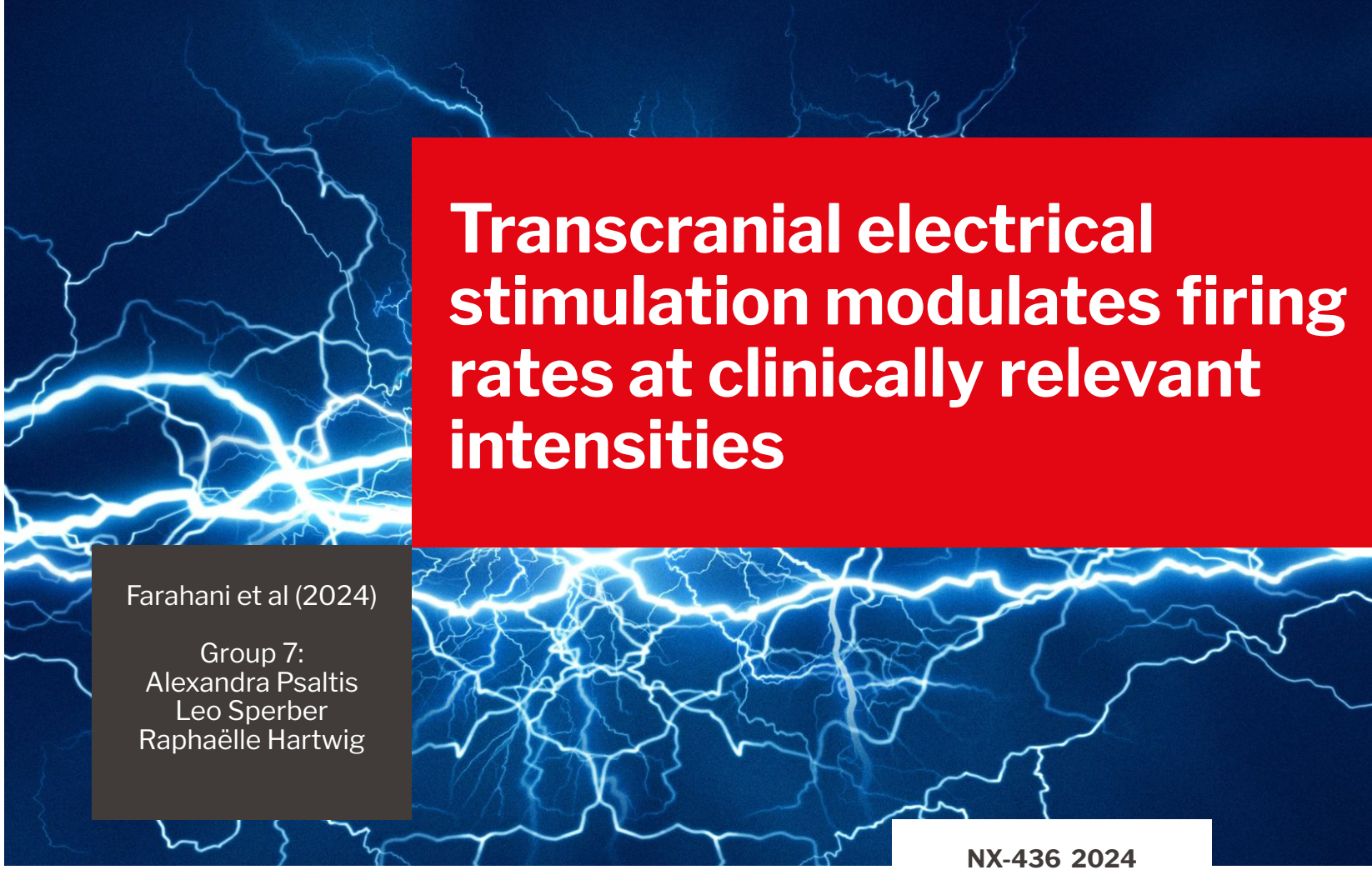


Transcranial electrical stimulation modulates firing rates at clinically relevant intensities

Farahani et al (2024)

Group 7:
Alexandra Psaltis
Leo Sperber
Raphaëlle Hartwig

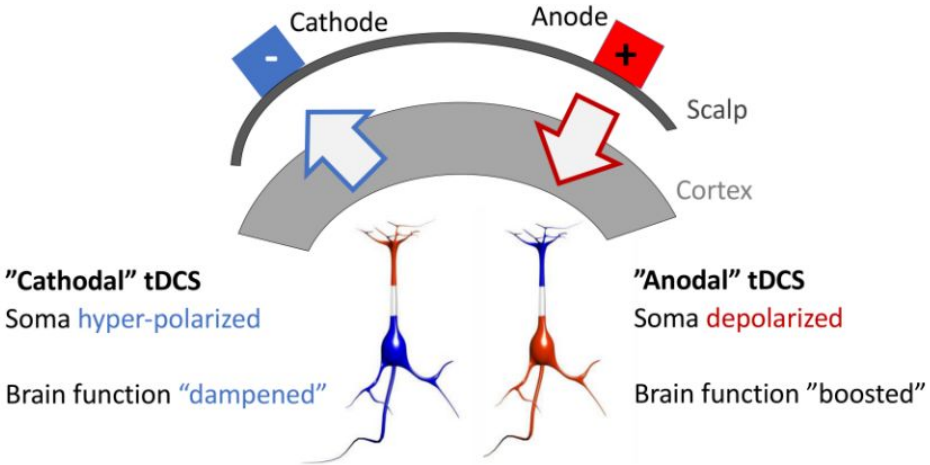
NX-436 2024

Introduction

Background on transcranial electrical stimulation and motivation for the study

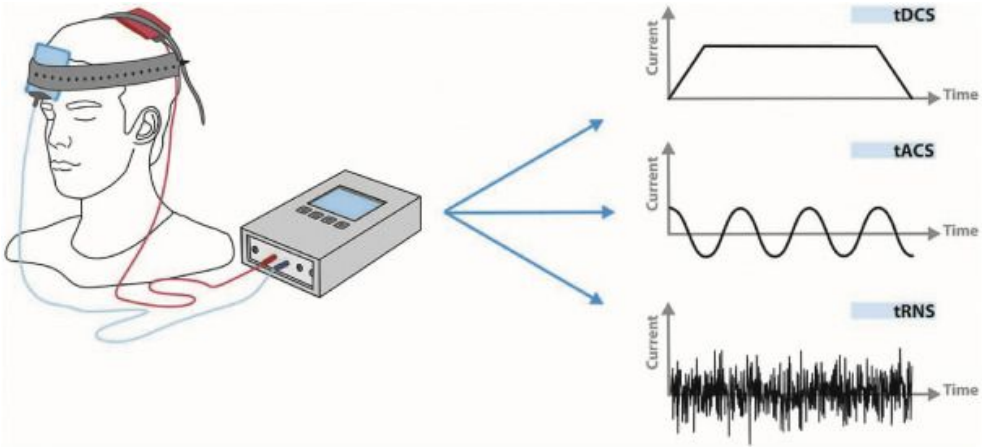
Transcranial Electrical Stimulation (tES)

- Non-invasive neuromodulation technique
- 2 electrodes on the skin generating electric fields, affecting neuronal membranes by acting on their polarization
- Excite or inhibit depending on the current



Transcranial Electrical Stimulation (tES)

- Transcranial direct current (tDCS), alternating current (tACS) or random noise (tRNS) stimulation



Clinical relevance of tES

- Problem: remains a critical gap in understanding efficacy and impact of low-intensity electric fields within a living brain
  - significant gap between electric fields
    - **in vivo in human** brain (<= 0.5 V/m)
    - **in vitro animal** experiments (>= 5 V/m)

- Question: can the low field intensities used in clinical settings induce measurable, relevant changes in neuronal behavior ?

Clinical relevance of tES

- Goal of study: investigate the effects of clinically relevant electric field strengths on hippocampal neurons in freely moving rats

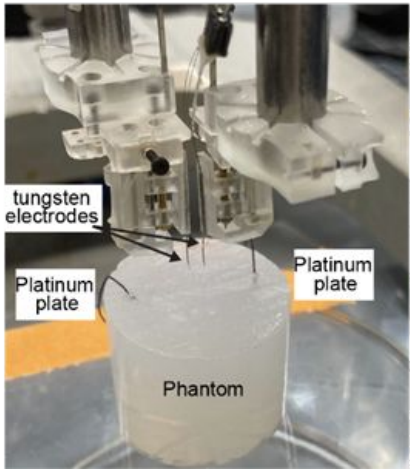
  1. Measure **electric fields magnitude** and their effects on neuronal firing rate in vivo in rats

  2. Establish **calibrated computational models of current flow** in motor cortex and hippocampus

Methods

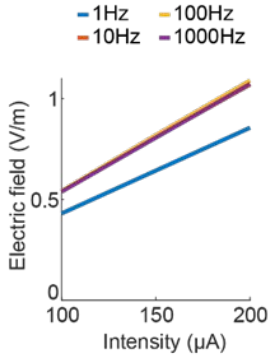
Techniques and methods used to ensure robustness of the study

Experiment preparation

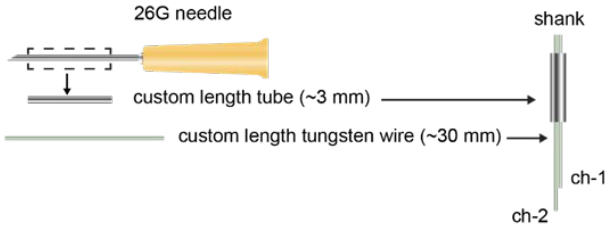


Equipment calibration with phantom brain

- Agar solution with T1 and T2 relaxation similar to gray matter
- Different frequencies (1, 10, 100, 1000 Hz)
- Different intensities (100, 150, 200 µA)
- Linear increase of electric field magnitude with stimulation intensity



Custom tungsten recording electrode



- 4 channel, 2 shank device
- Record electric field magnitude
- Attached to mechanical shuttle (microdrive)

Computational models

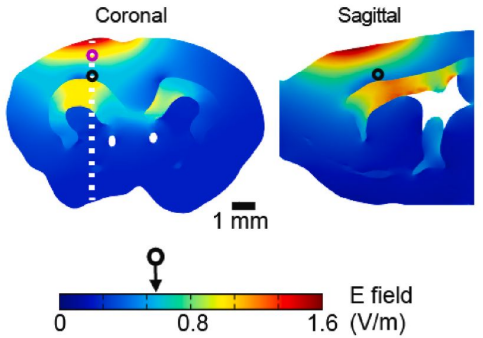
Electric field prediction

- Conductor model based on segmented MRI rat head scan
- Electrodes placed according to experiment coordinates
- Mesh of rat model imported in COMSOL

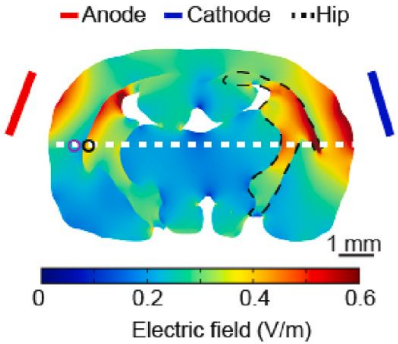
COMSOL MULTIPHYSICS®

- Finite element analysis software
- Literature based conduction values for each head compartment
- 2D simulation of brain slice

Montage 1:

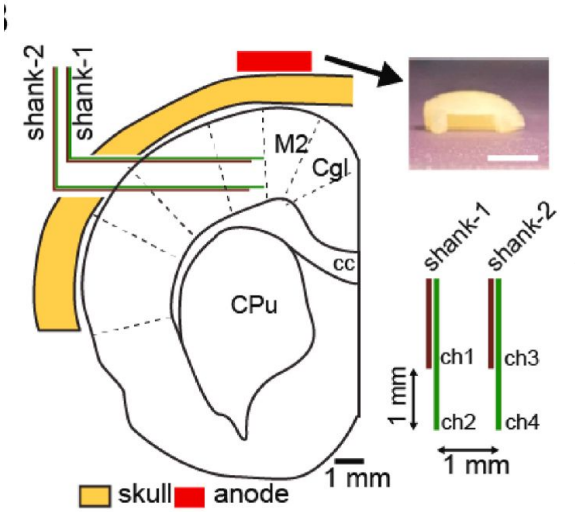


Montage 2:

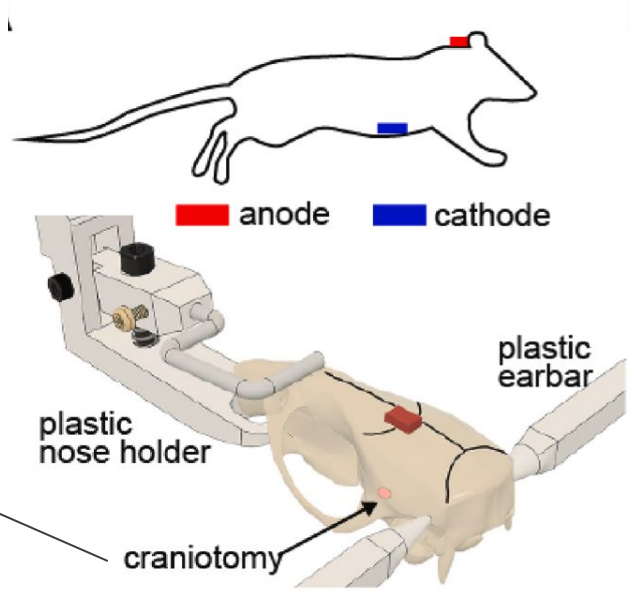


Experimental setup on anesthetized rats (montage 1)

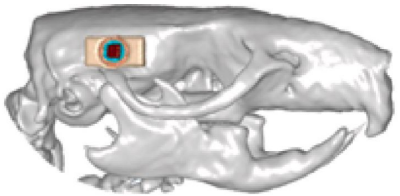
- Motor cortex stimulation and recording
- Varying frequency (10, 100, 1000 Hz)
- Varying intensity (10, 20, 40 µA)



Montage 1 electrode placement and setup:



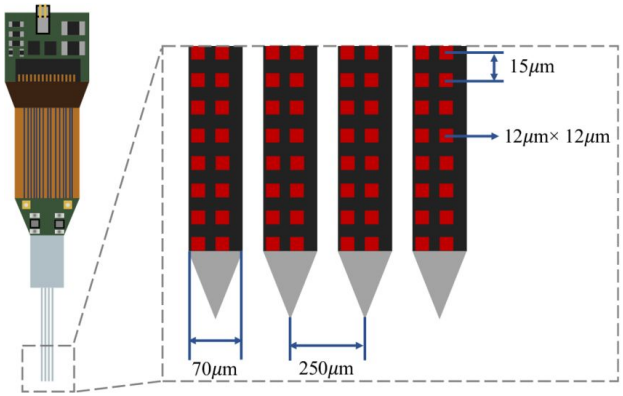
Experimental setup on freely moving rats (montage 2)

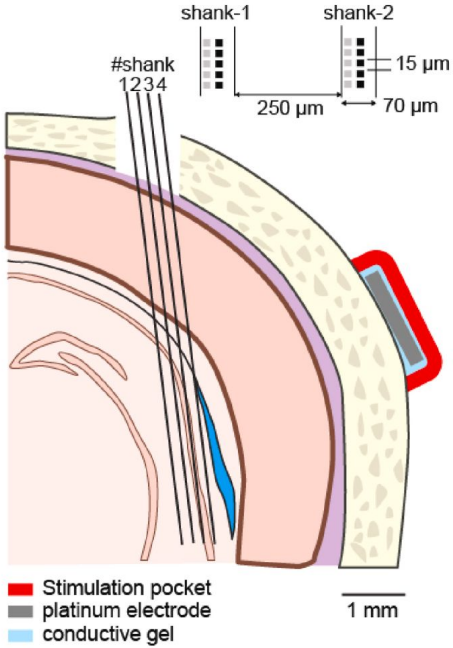


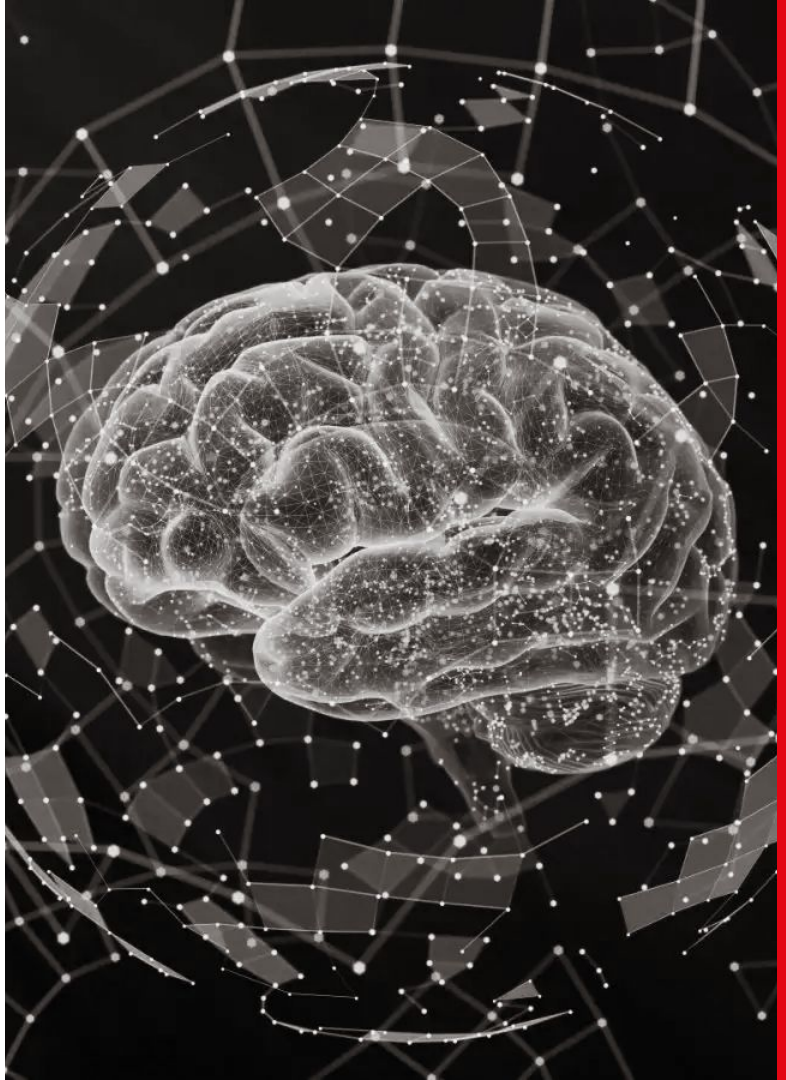
- Symmetrical (sagittal plane) electrode placement on temporal bone
- Varying frequency (10, 100, 1000Hz)
- Varying intensity (10, 20, 30 µA)
- Direct current for single unit recording (3-4s bursts)

Neuropixels 2.0:

- 4 shanks
- 5120 recording sites
- 384 channels per probe
- Implanted in intermediate CA2 region



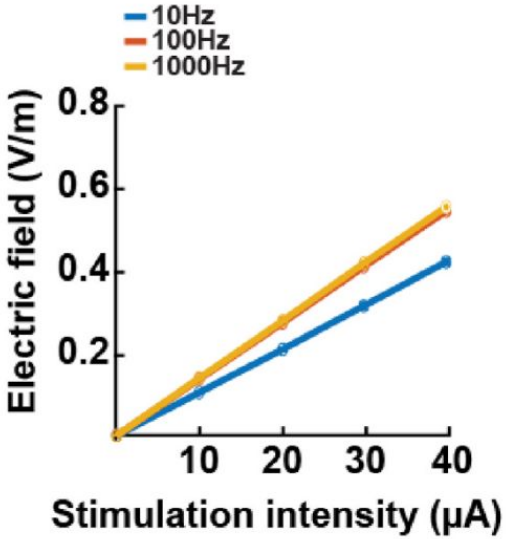


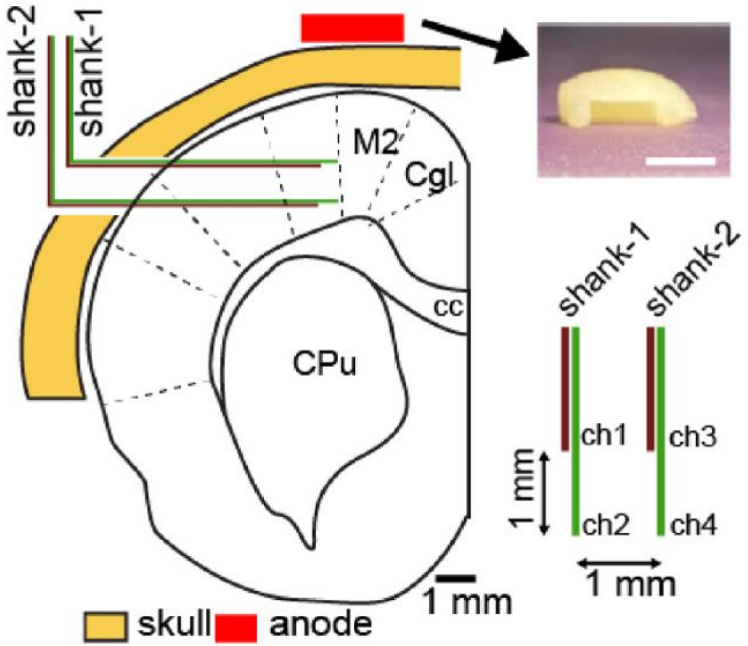


Results

Presentation and analysis of experiment results

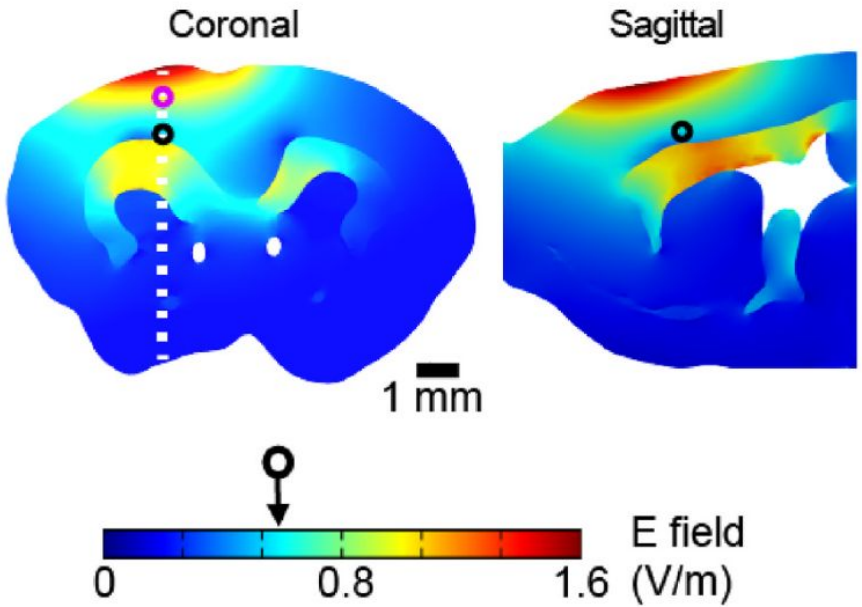
Electric field magnitude increases linearly with applied current in the motor cortex





Slope average on all three = 15 V/m

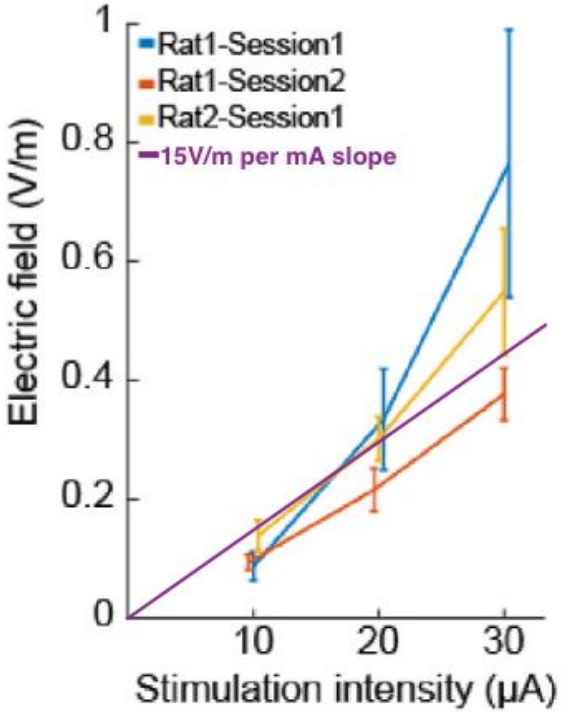
Computational model results are consistent with in-vivo results in the motor cortex



Model prediction in motor cortex at 40 µA current: 0.602 V/m

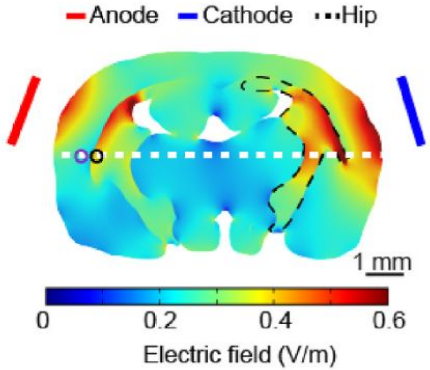
This is equal to 15.05 V/m per mA

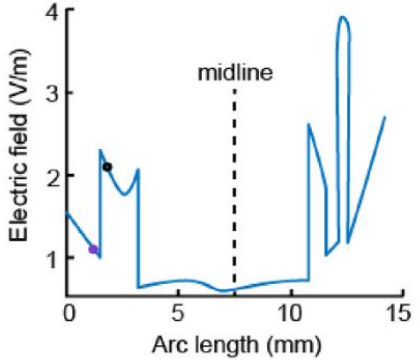
Electric field magnitude increases approximately linearly with applied current in the hippocampus



- The slope corresponds to 10, 14 and 18.7 V/m per mA (average = 14.23 V/m per mA)
- Variation in tissue conductivity and structure between hippocampus and cortex leads to weaker electric field for the same amount of current.
- They assume 15 V/m per mA in the hippocampus for the remainder of the paper

Computational model results are approximately consistent with in-vivo results in the hippocampus



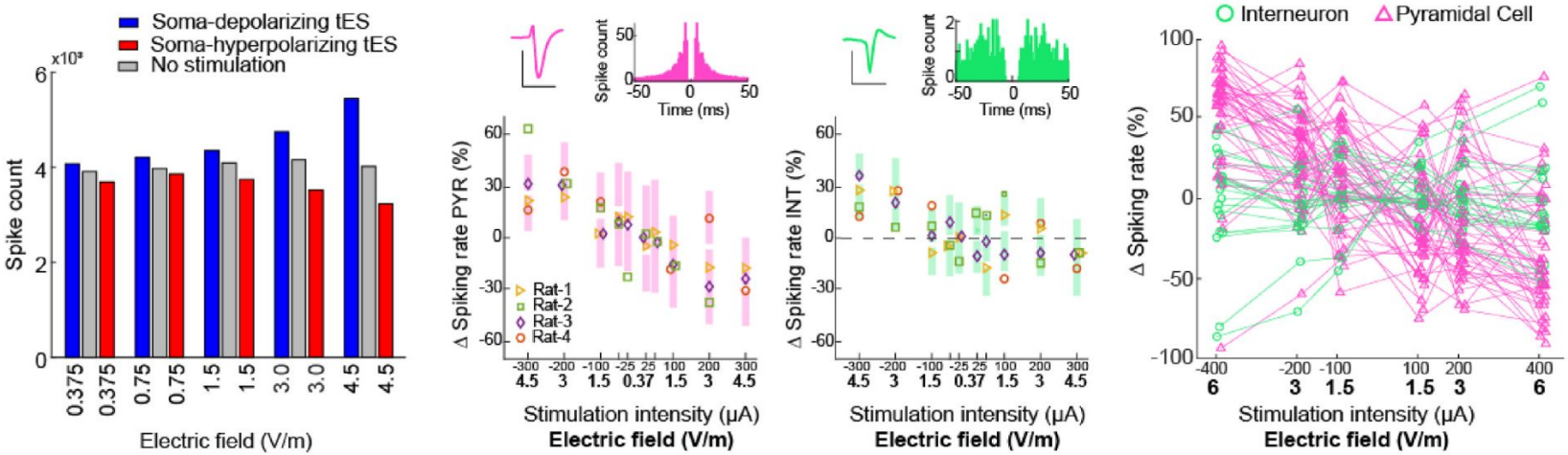


Model prediction in white matter: 2.1 V/m (= 21V/m per mA)

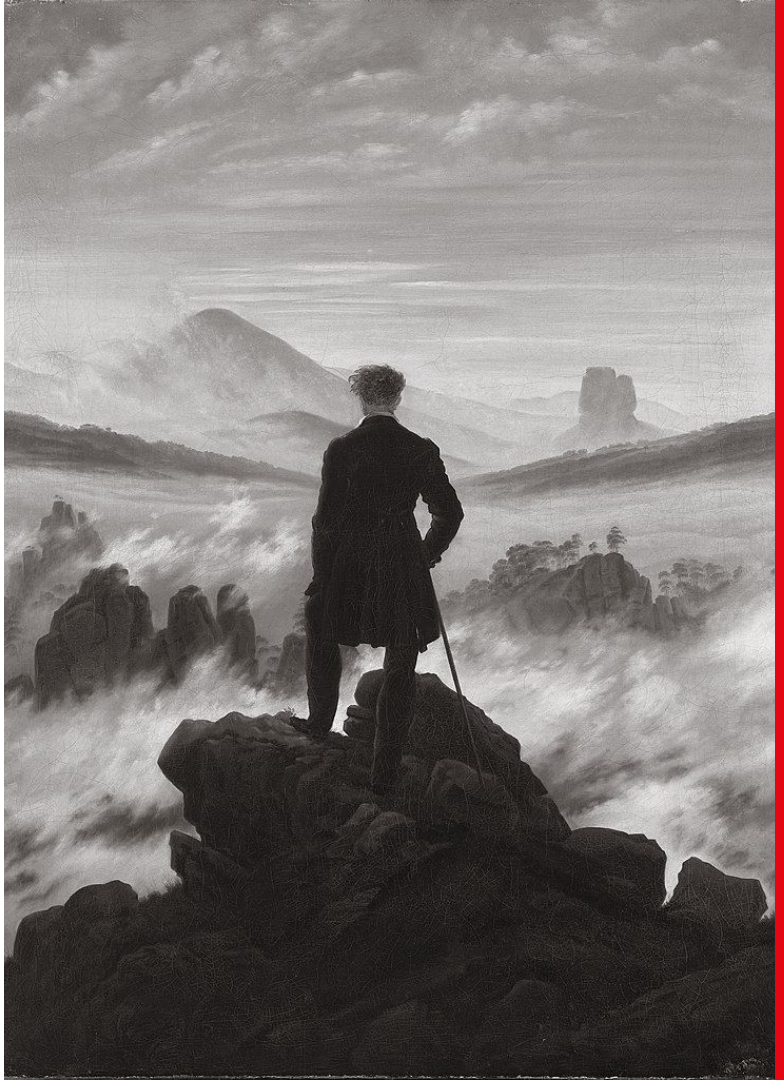
Model prediction in grey matter: 1.2 V/m (= 12 V/m per mA)

Anatomical structure influenced the distribution of electric fields across the hippocampus (discontinuity in conductance between white and grey matter)

Polarity-dependent changes in firing rates in the hippocampus



- The firing rate of excitatory neurons increased with soma-depolarizing stimulation and decreased with soma-hyperpolarizing stimulation



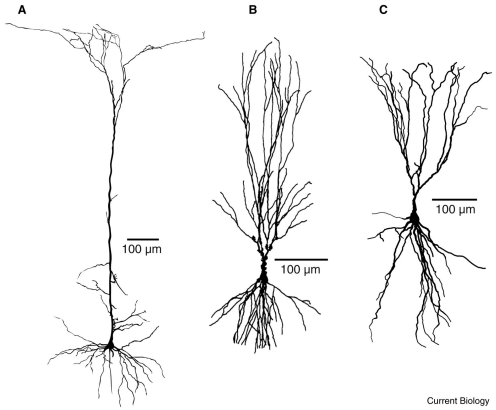
Discussion

Contribution of the study to our understanding of transcranial electrical stimulation

Electric field effect on neurons

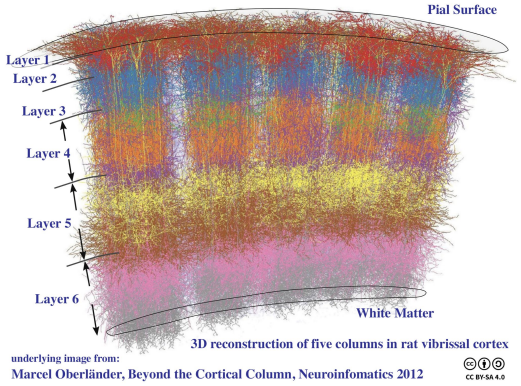
Key findings:

- Low intensity electric fields (~0.5 V/m) can modulate neuronal firing rates in vivo at clinically relevant levels
- Pyramidal neuron orientation make them particularly sensitive to field orientation
- Interneurons have a more varied response, likely due to network connectivity



Implications for clinical tES:

- Aligning field orientation with cell structures in specific brain regions optimizes neuromodulatory impact
- Researching further synaptic plasticity response at low-intensity fields could guide tES paradigms for clinical application



For further research

Bridging the gap between animal and human study

Estimates suggest field intensities can be ten times stronger in animals compared to humans

The study suggests for any animal tES study:

- Measuring electric field using sinusoïdal waveforms at three different intensities
- Calibrating equipment using a phantom

Limitations and future challenges

Short term focus on acute effects:

Limitation: The study measured neuronal firing rates during short bursts of electrical stimulation (3-4s)

Challenge: Explore cumulative effect of repeated tES stimulation on synaptic plasticity

Focus on single brain region (Hippocampus):

Limitation: Neuronal orientation varies across brain regions, effects observed may not translate to other regions

Challenge: Extending experiments to other brain regions to generalize findings

Other possible directions:

- Integrating behavioral tests
- Increase sample size
- Human translation

Brain Stimulation 17 (2024) 561–571

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: www.journals.elsevier.com/brain-stimulation

Transcranial electric stimulation modulates firing rate at clinically relevant intensities

Forouzan Farahani [a], Niranjan Khadka [a], Lucas C. Parra [a], Marom Bikson [a], Mihály Vöröslakos [b,*]

[a] Department of Biomedical Engineering, The City College of New York, New York, NY, USA
[b] Neuroscience Institute and Department of Neurology, NYU Grossman School of Medicine, New York University, New York, NY, USA

ARTICLE INFO

Keywords:
Transcranial electric stimulation
Computational modeling
Single-unit effects

ABSTRACT

Background: Notwithstanding advances with low-intensity transcranial electrical stimulation (tES), there remain questions about the efficacy of clinically realistic electric fields on neuronal function.
Objective: To measure electric fields magnitude and their effects on neuronal firing rate of hippocampal neurons in freely moving rats, and to establish calibrated computational models of current flow.
Methods: Current flow models were calibrated on electric field measures in the motor cortex (n = 2 anesthetized rats) and hippocampus. A Neuropixels 2.0 probe with 384 channels was used in an in-vivo rat model of tES (n = 4 freely moving and 2 urethane anesthetized rats) to detect effects of weak fields on neuronal firing rate. High-density field mapping and computational models verified field intensity (1 V/m in hippocampus per 50 μA of applied skull currents).
Results: Electric fields of as low as 0.35 V/m (0.25–0.47) acutely modulated average firing rate in the hippocampus. At these intensities, firing rate effects increased monotonically with electric field intensity at a rate of 11.5 % per V/m (7.2–18.3). For the majority of excitatory neurons, firing increased for soma-depolarizing stimulation and diminished for soma-hyperpolarizing stimulation. While more diverse, the response of inhibitory neurons followed a similar pattern on average, likely as a result of excitatory drive.
Conclusion: In awake animals, electric fields modulate spiking rate above levels previously observed in vitro. Firing rate effects are likely mediated by somatic polarization of pyramidal neurons. We recommend that all future rodent experiments directly measure electric fields to insure rigor and reproducibility.

1. Introduction

The effects of transcranial electric stimulation on neural activity in the brain have been known since the 1960 [1–3]. The acute effects on neuronal firing rate are particularly well established. Namely, the electric fields generated within the brain by transcranial current stimulation can incrementally polarize cell membranes [4] and thus modulate ongoing cell firing [5,6]. The effect acts at the time scale of the neuronal membrane (~30 ms) and thus is relevant for direct current (DC) and most effective for alternating currents (AC) of 30 Hz or less [7,8]. This acute neuromodulatory effect can be predicted from the orientation and intensity of local electric fields [9,10]. These cellular mechanisms established with in vitro animal experiments, also point to network effects [11,12], which can be properly studied only in the intact brain.

However, despite numerous in-vivo animal studies in the intervening decades [12–24], there is still a lack of clarity as to whether the effects observed are clinically relevant, for one simple reason: in vivo animal experiments have not adequately characterized electric field magnitudes in the brain. In particular, a significant gap has emerged [25] between electric fields measured in vivo in the human brain, which are at or below 0.5 V/m [19,26,27] and field intensities used for in vitro animal experiments, which are mostly at or above 5 V/m [28]. Thus, it is difficult to interpret and link results from in vivo animal experiments to cellular effects observed in vitro. Nor is it clear that the in vivo animal experiments have any relevance to the behavioral effects observed in human clinical studies.

To close this gap, we measured electric fields magnitude and their effects on neuronal firing rate in vivo in rats and established calibrated computational models of current flow. To do so, we first calibrated our recording equipment on a phantom, and performed in vivo field measurements in cortex and hippocampus in a rodent tES model. Then, using

* Corresponding author.
E-mail address: mihaly.voroslakos@nyulangone.org (M. Vöröslakos).

https://doi.org/10.1016/j.brs.2024.04.007
Received 20 December 2023; Received in revised form 25 March 2024; Accepted 11 April 2024

Conclusion