Transcranial electrical stimulation (TES) induced synaptic plasticity in freely moving rats

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Translational Research in Progress (TRIP) Seminar
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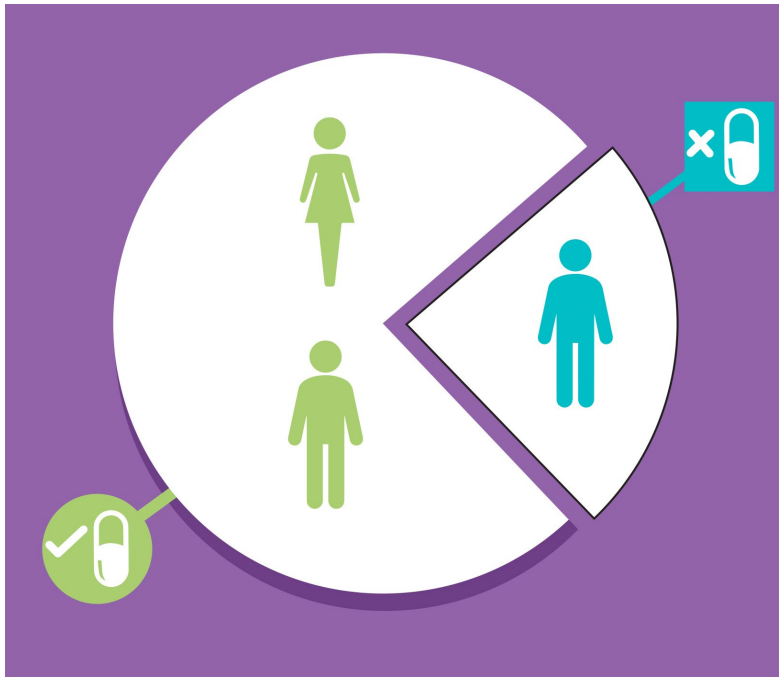
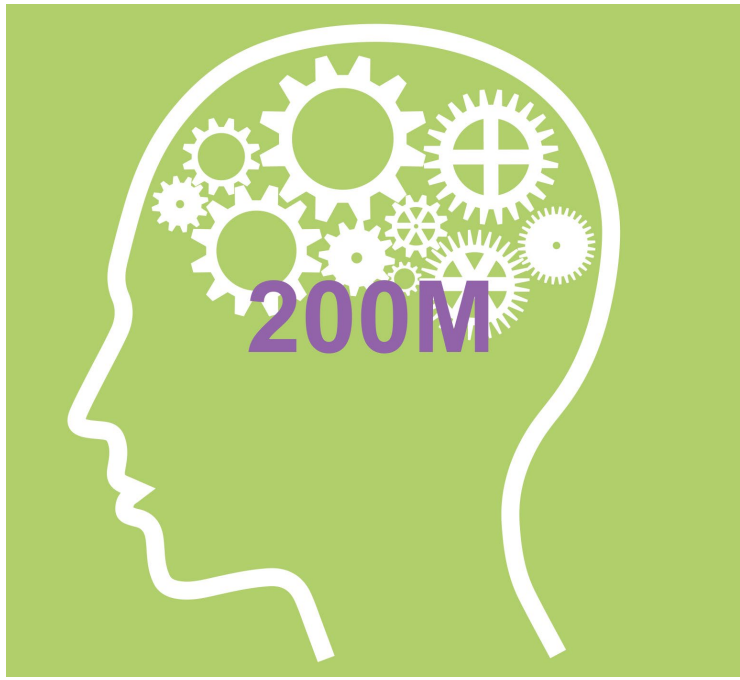
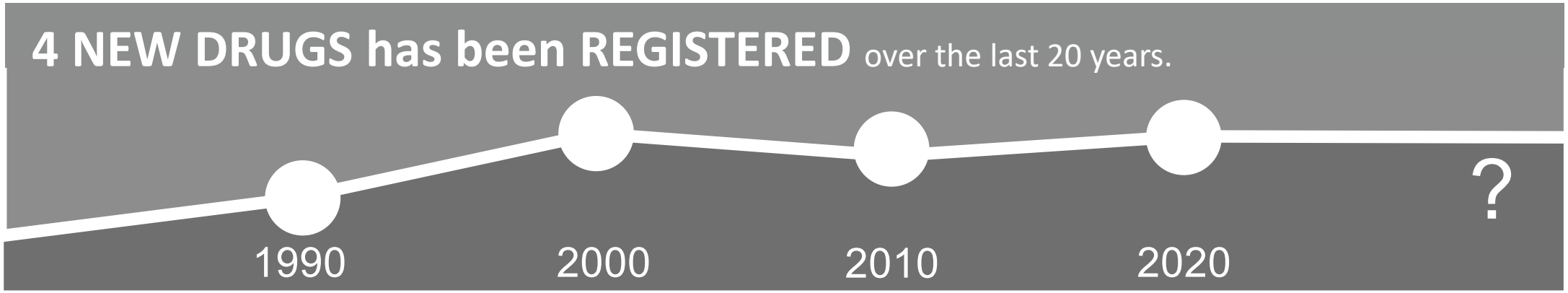
Neurological and psychiatric disorders in numbers







Source: WHO

Big pharma is leaving neuroscience

AstraZeneca 2016

Pfizer 2018

Amgen 2019

ENDPOINTS NEWS

July 20, 2016 09:55 AM EDT
R&D

AstraZeneca culls its neuroscience team, exits Kendall Square office

John Carroll
Editor & Founder

NEWS & ANALYSIS

Nature Reviews Drug Discovery | Published online 1 Feb 2018

NEWS IN BRIEF

Pfizer exits neuroscience

Asher Mullard

BIOPHARMA DIVE

DIVE BRIEF

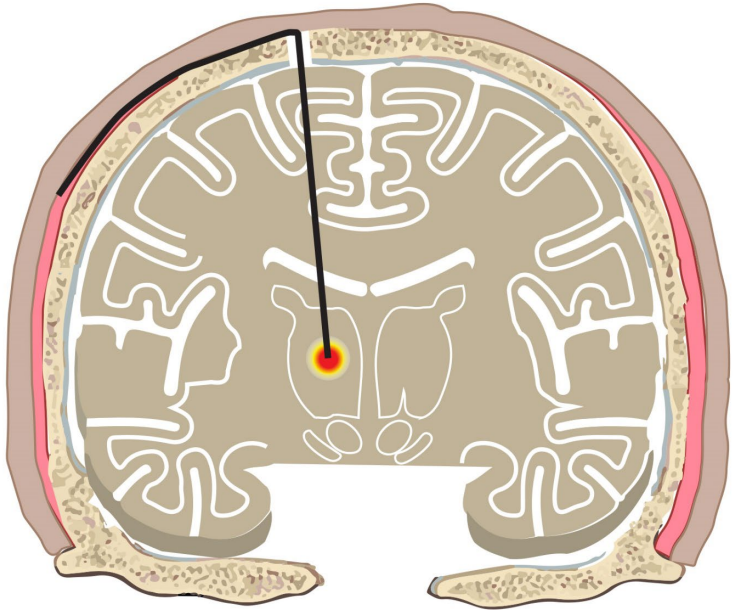
Amgen exits neuroscience R&D as pharma pulls back from field

Published Oct. 30, 2019

Neuromodulation techniques

DBS

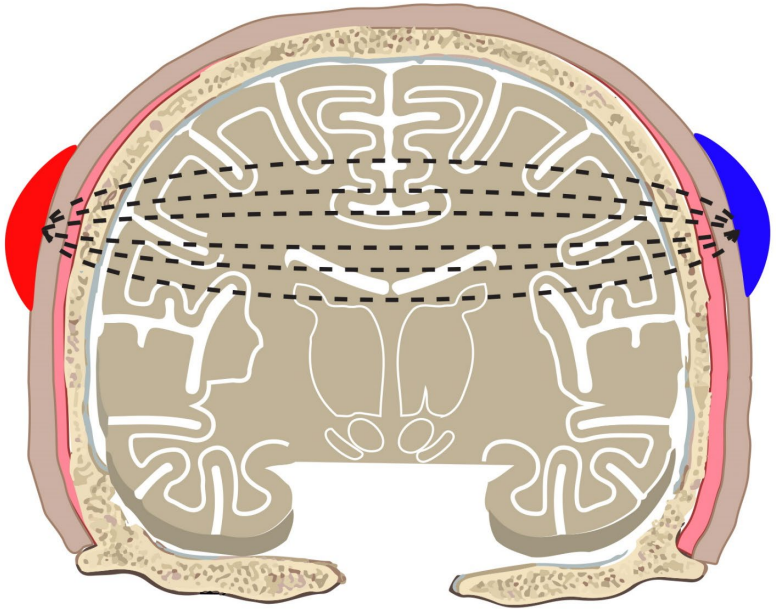
Deep brain stimulation



Invasive
Excellent spatial resolution
Depth can be stimulated

TES

Transcranial electrical stimulation



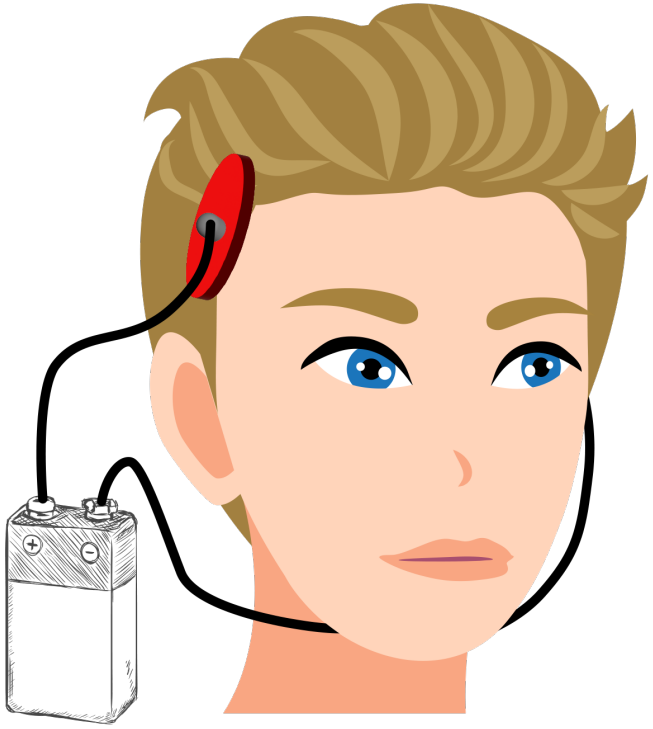
Non-invasive
Poor spatial resolution
Depth cannot be stimulated
Inexpensive

Scangos et. al., 2021, Nat. Medicine

Transcranial direct current stimulation (tDCS)

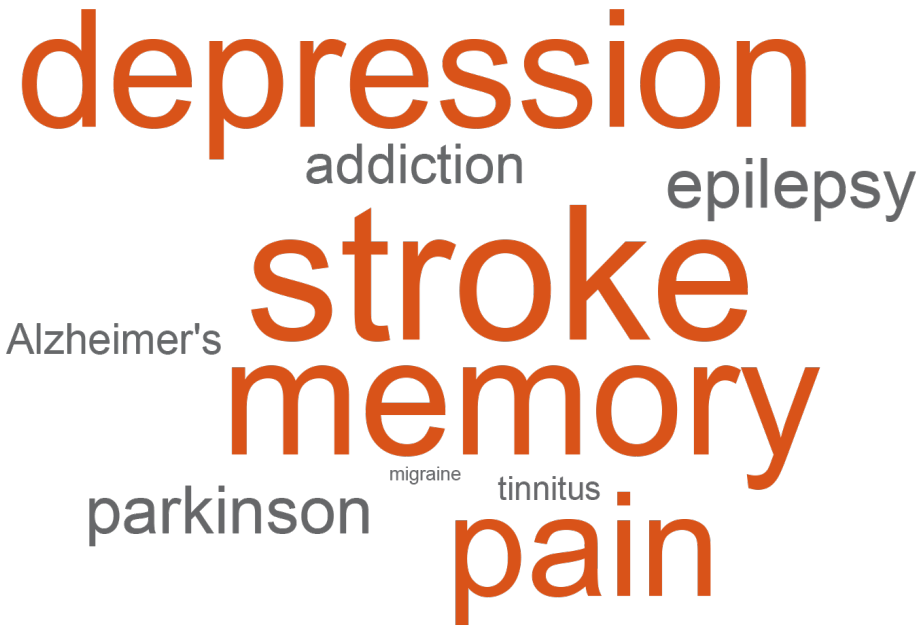
Stimulation parameters

- *Waveform:* direct current
- *Intensity:* Low (< 2mA)
- *Duration:* 10 – 20 minutes



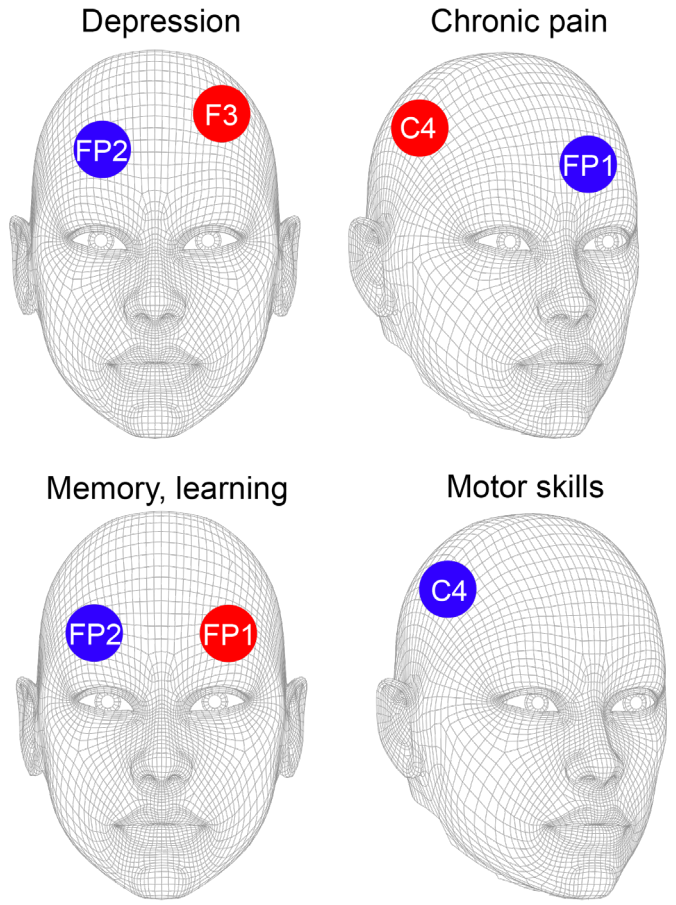
Anode Cathode

tDCS in clinical trials



Based on PubMed search tDCS AND disorderName

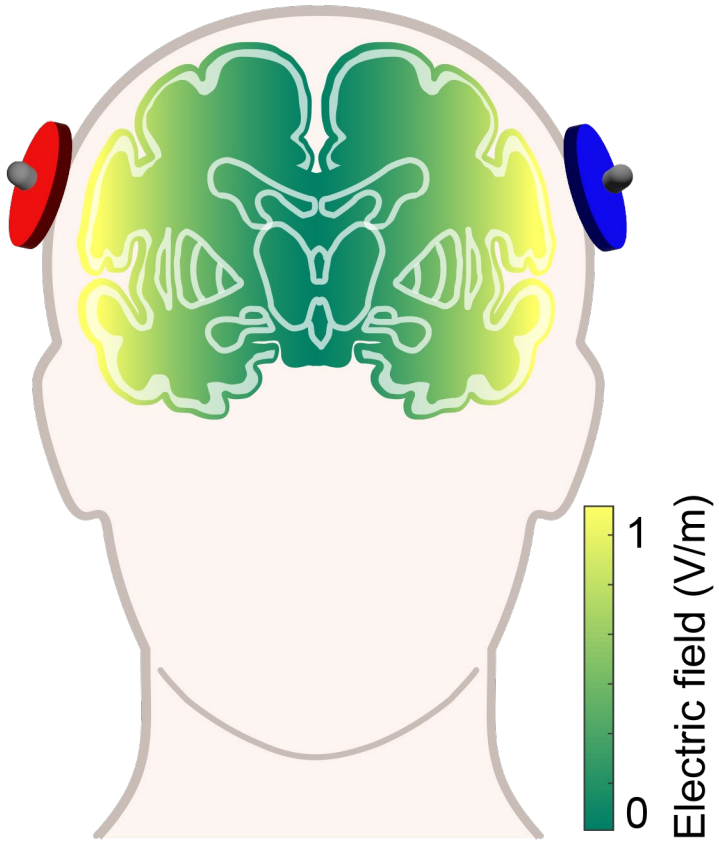
Electrode montage



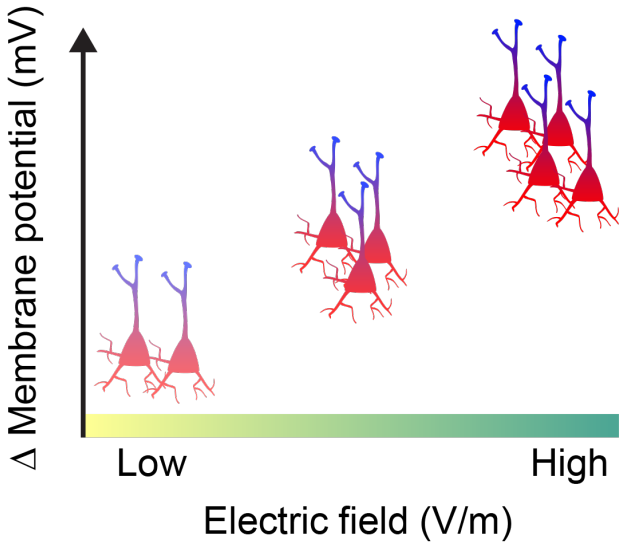
Effects of tDCS

Effects depend on

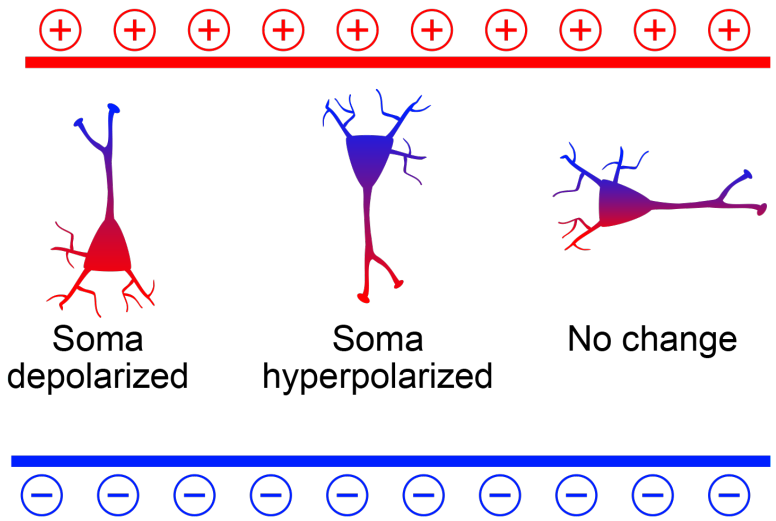
- Electrode *location, size and configuration*
- Stimulation *polarity, intensity and duration*
- Target area *depth, neurons' morphology*



Effect of electric field strength

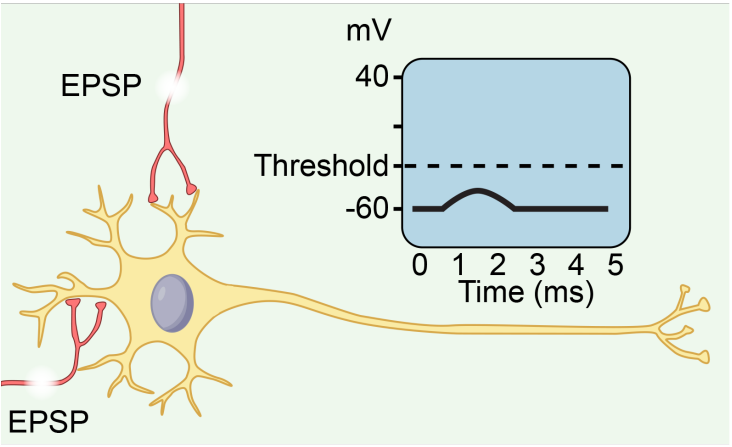


Orientation / morphology of neuron

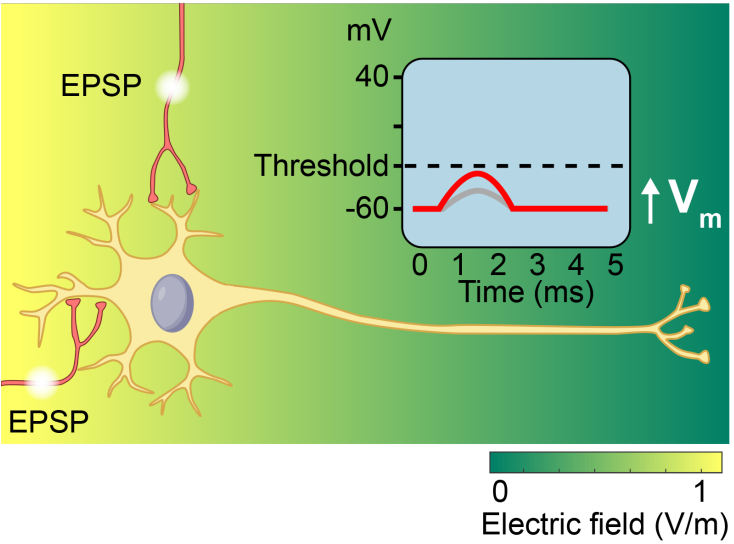


Liu et. al., 2018, Nat. Comm.

Effects of tDCS



Normal activity



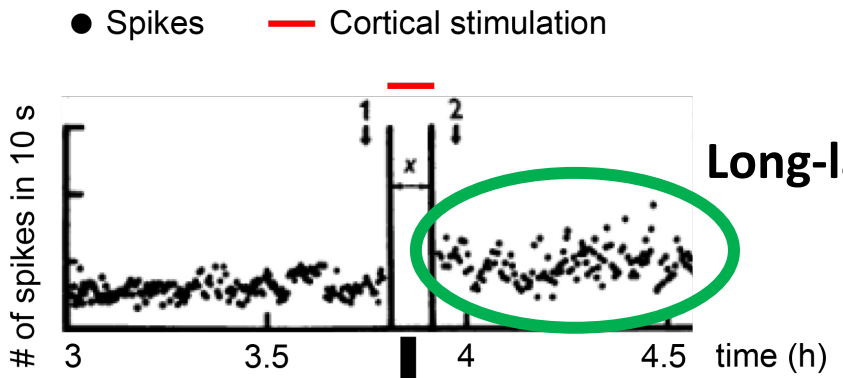
tDCS

↓ **Electric field**

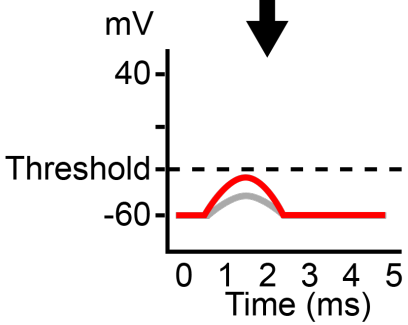
Change in V_m (subthreshold)

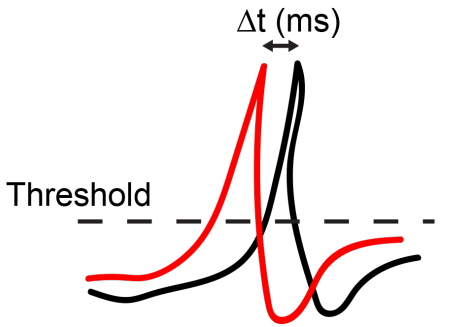
↓

Change in AP timing



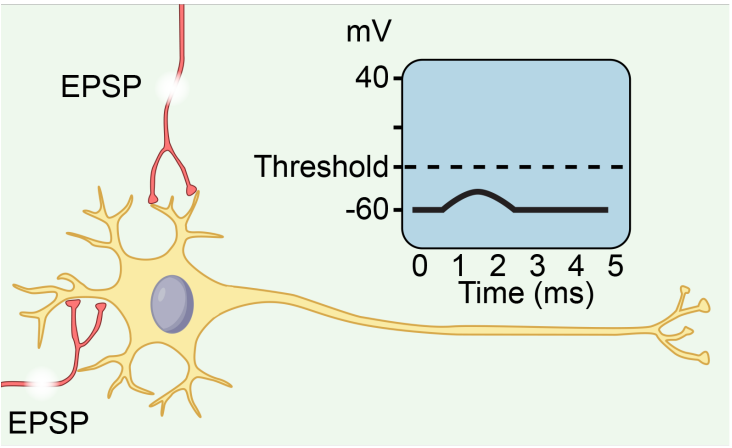
Long-lasting effects





Bindman et. al., 1962

Origins of tDCS-induced neuroplasticity



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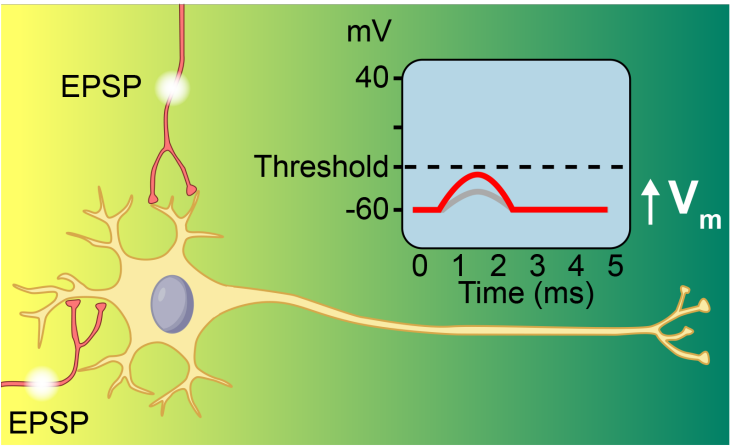


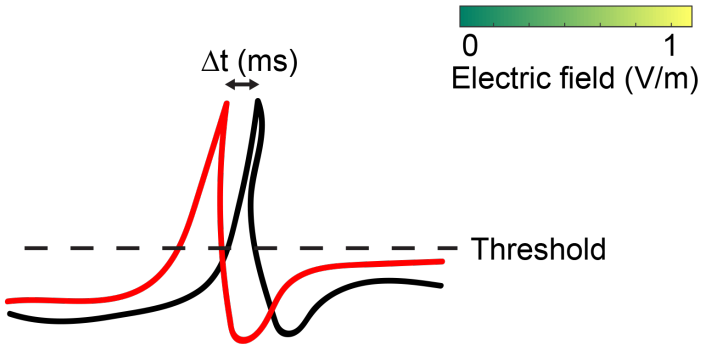
tDCS

↓ **Electric field**

Change in V_m (subthreshold)

↓

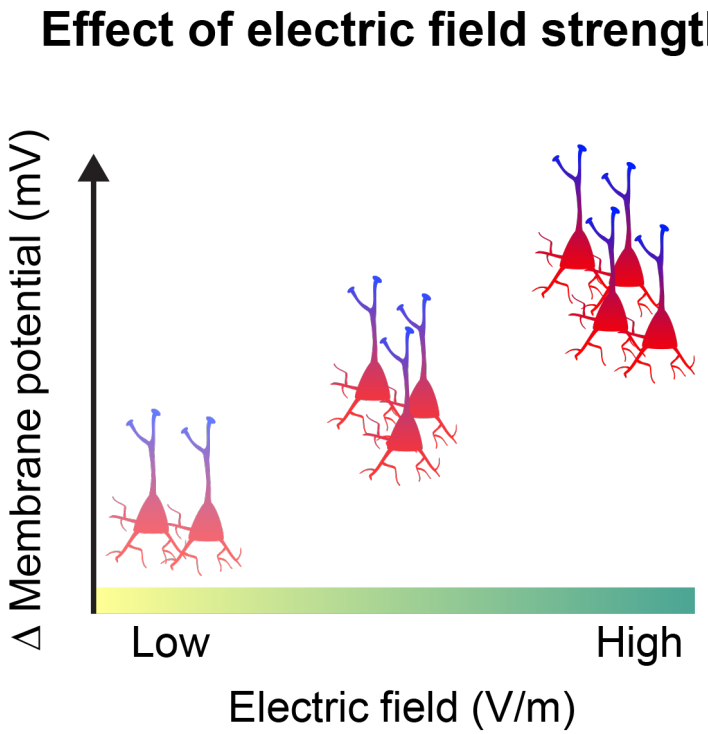
Change in AP timing



Polarization of soma

1. **Hebbian reinforcement** (clinically combining tDCS with a cognitive task)
2. **Associative learning** (clinically combining tDCS with training)
3. **Non-synaptic origin**

Cellular targets of tDCS in animal studies

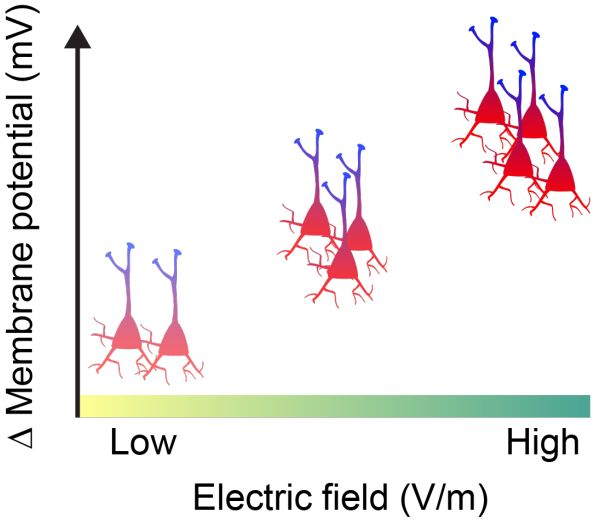


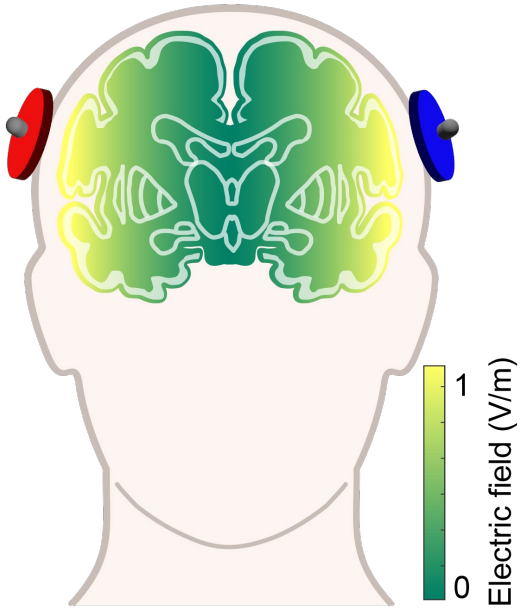
10 - AMPA trafficking
9 - Protein synthesis
8 - mGluR5
7 - Adenosine A1R
6 - BDNF
5 - Oscillation Power
4 - NMDAR
3 - LTD
2 - LTP
1 - Firing rate

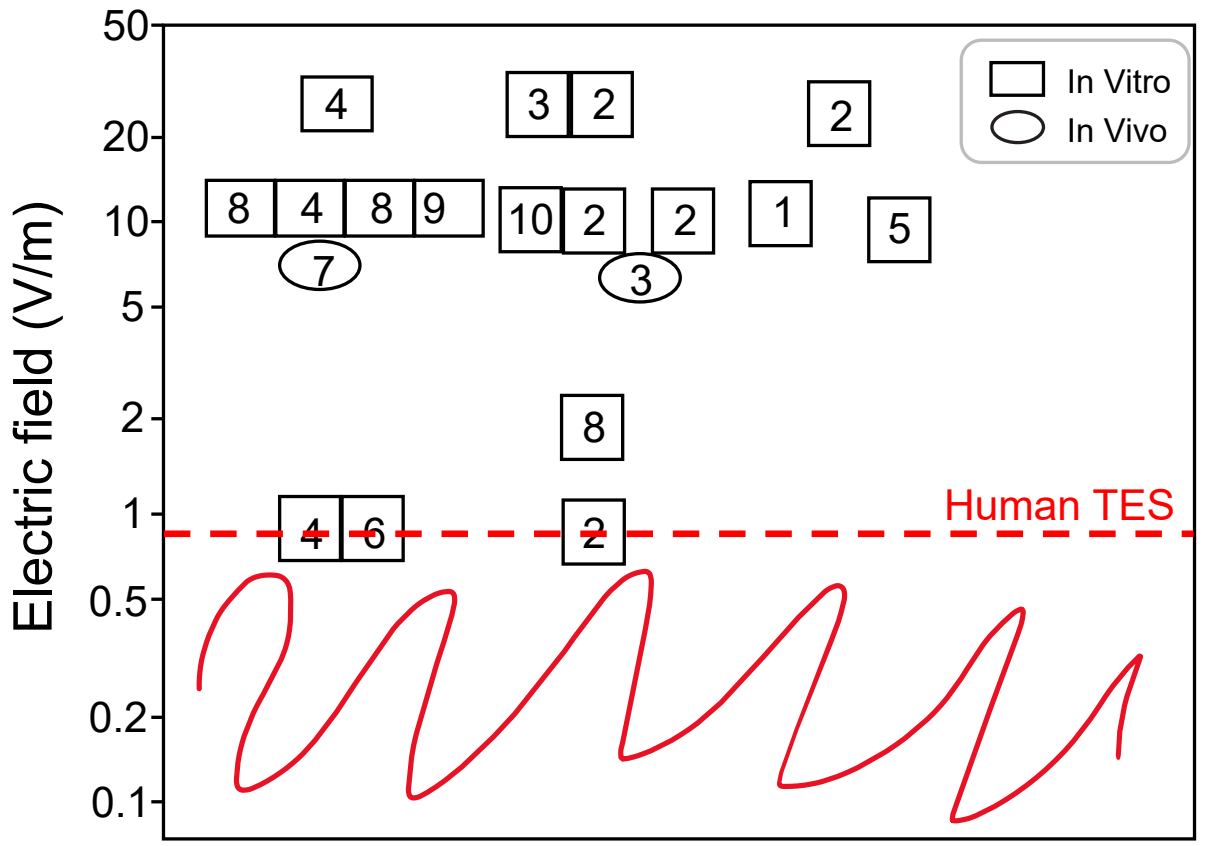
Courtesy of Dr. Greg Kronberg.

Cellular targets of tDCS in animal studies

Effect of electric field strength







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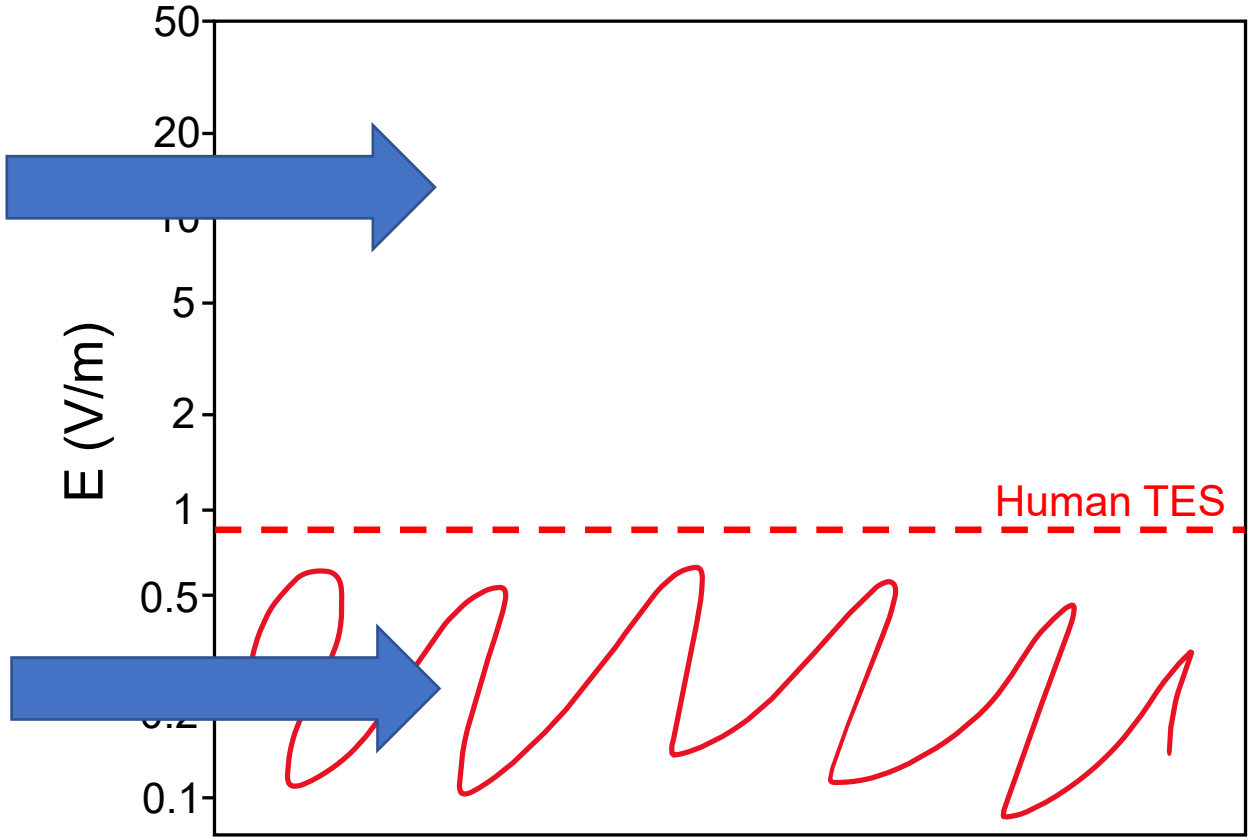
IS HUMAN TRANSLATION POSSIBLE?

Courtesy of Dr. Greg Kronberg.

Is human translation possible?

Increase electric field in humans (painful)

Decrease electric field in animals



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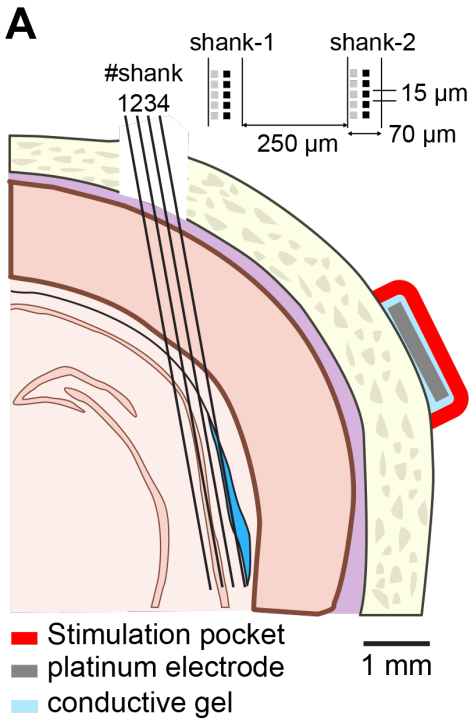
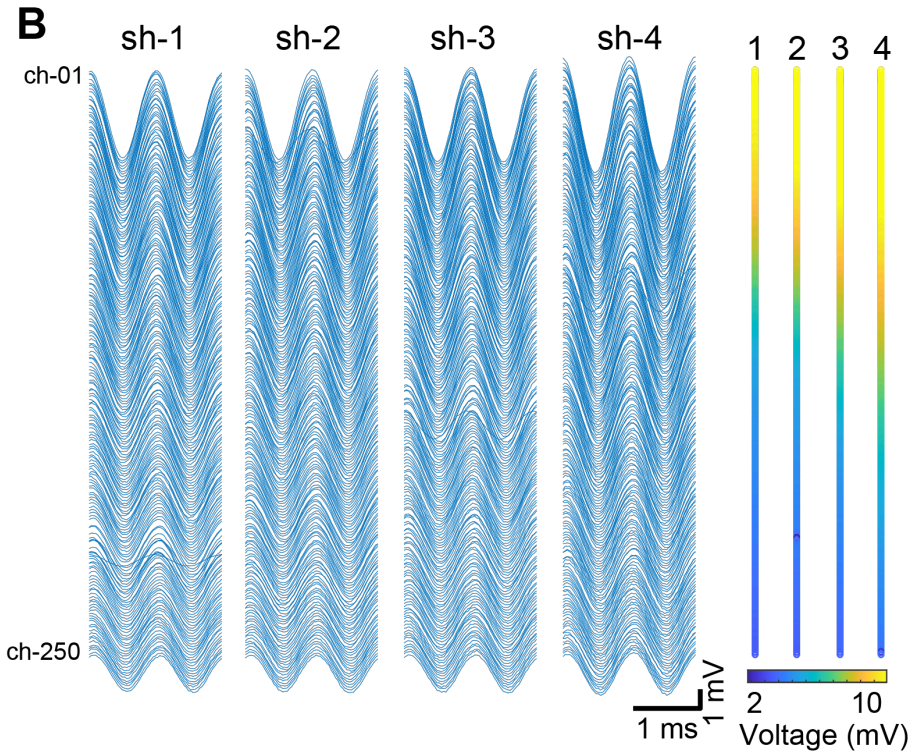
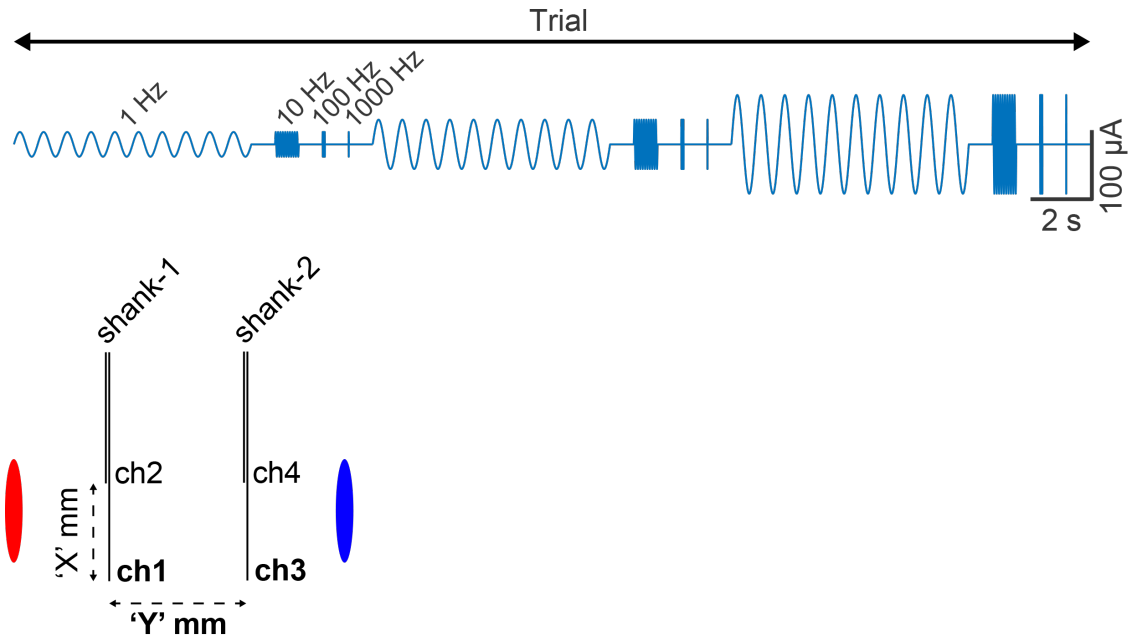
Courtesy of Dr. Greg Kronberg.

Measuring electric fields in rats





How can we measure electric fields?



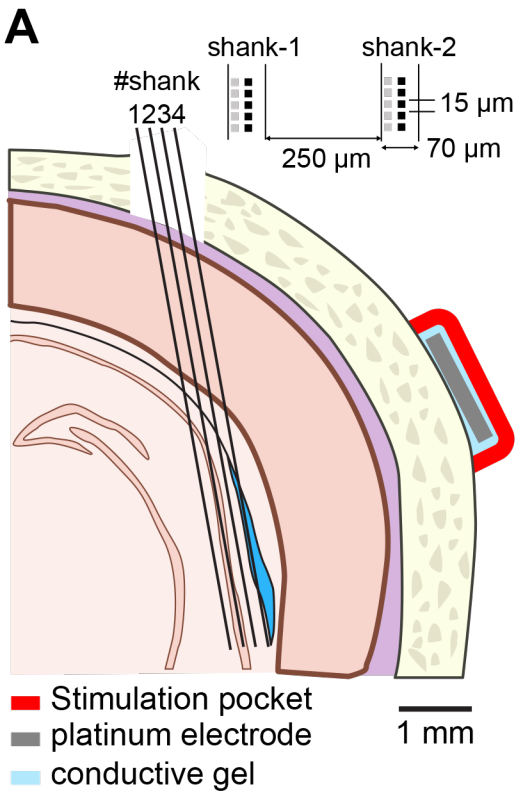
Neuropixels 2.0

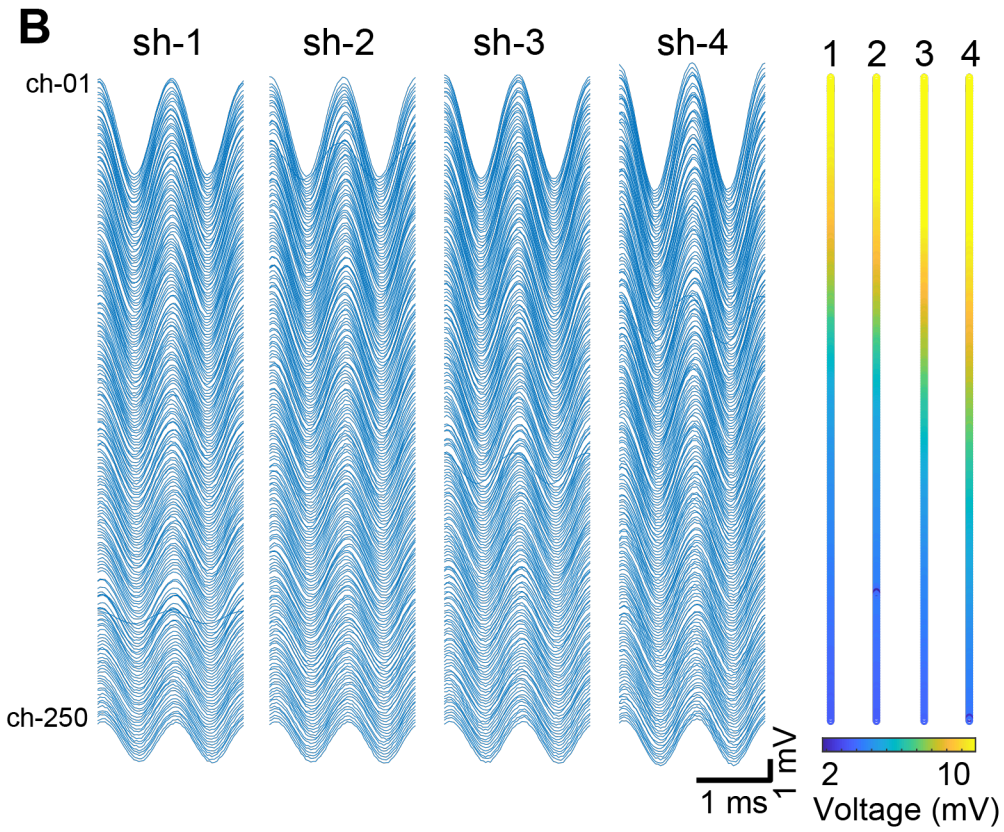
- 1280 recording sites / shank

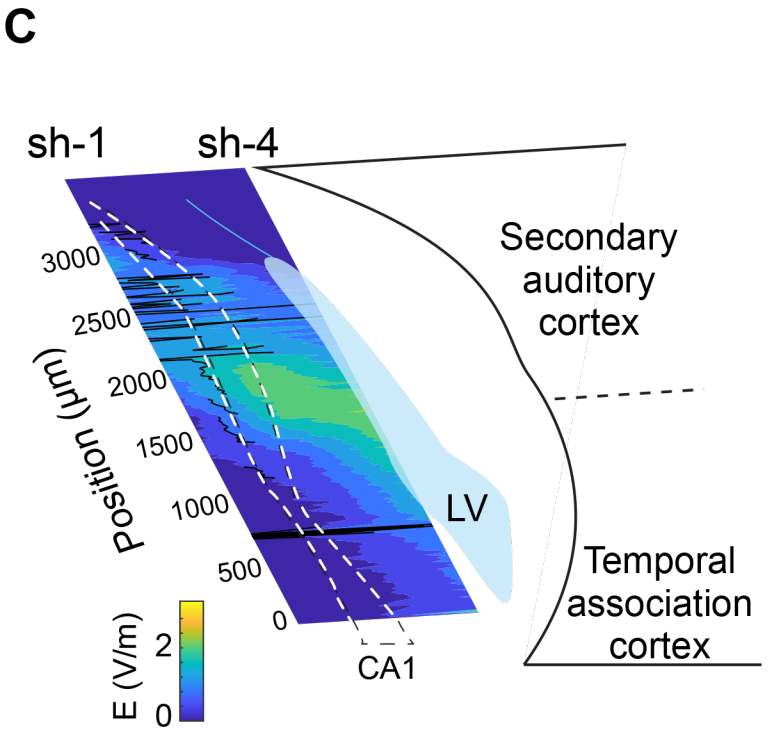
Shank-by-shank recording

- 4 x 384 channels = 1536 channels

Stimulation induced electric fields in rats







Neuropixels 2.0

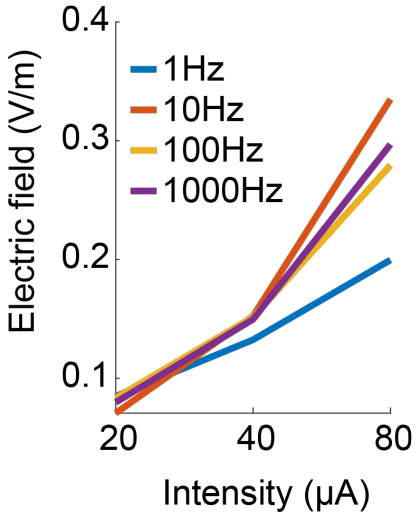
- 1280 recording sites / shank

Shank-by-shank recording

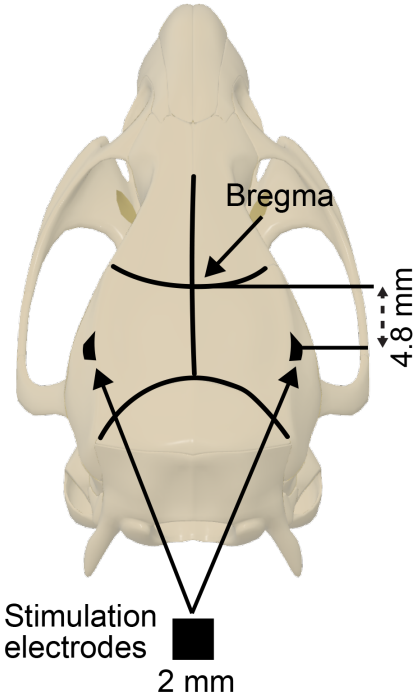
- 4 x 384 channels = 1536 channels

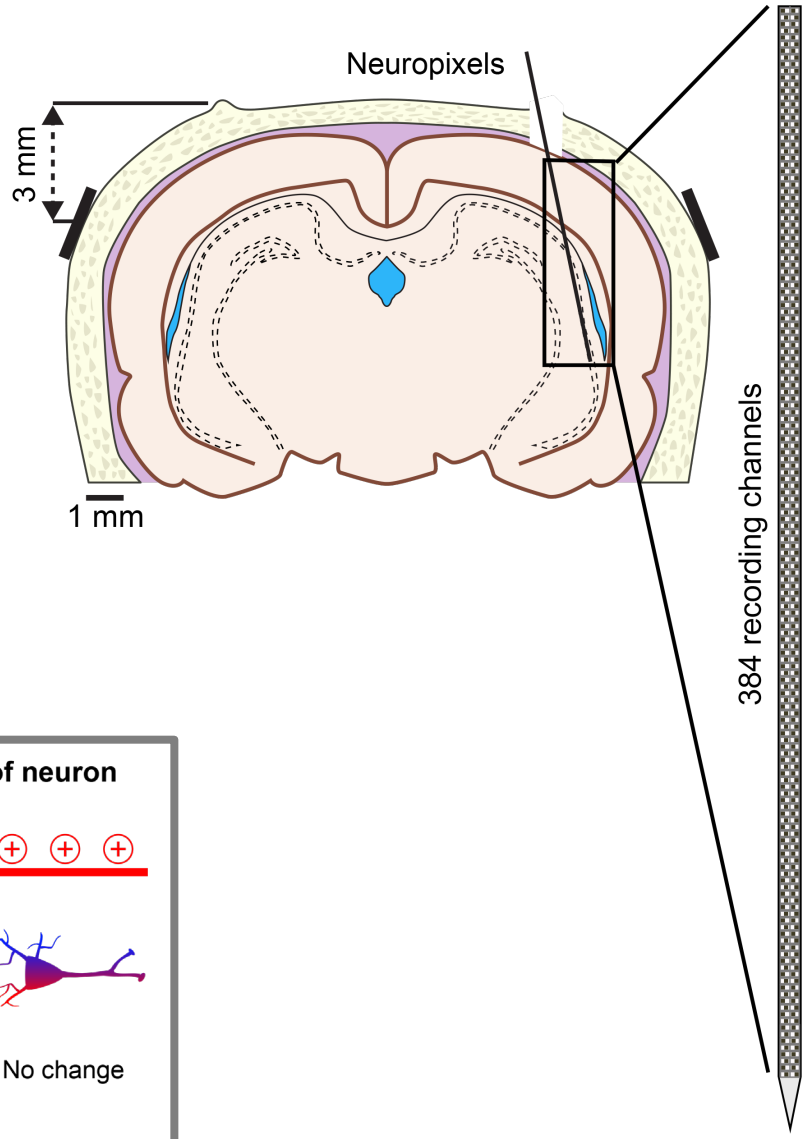
0.35 V/m @ 80 µA

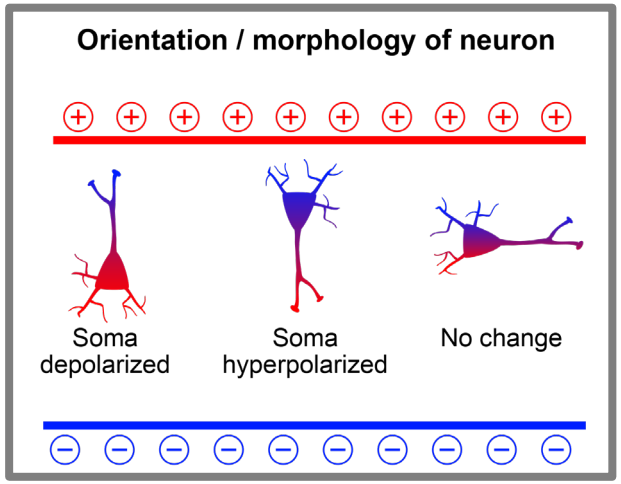
Human limit < 200 µA



tDCS-induced neuroplasticity in rats - Methods







Effects of tDCS depend on

Stimulating electrode *location and size*

- Fixed across animals

Low variability

Stimulation *polarity, intensity and duration*

- Varied across days

Test multiple tDCS parameters

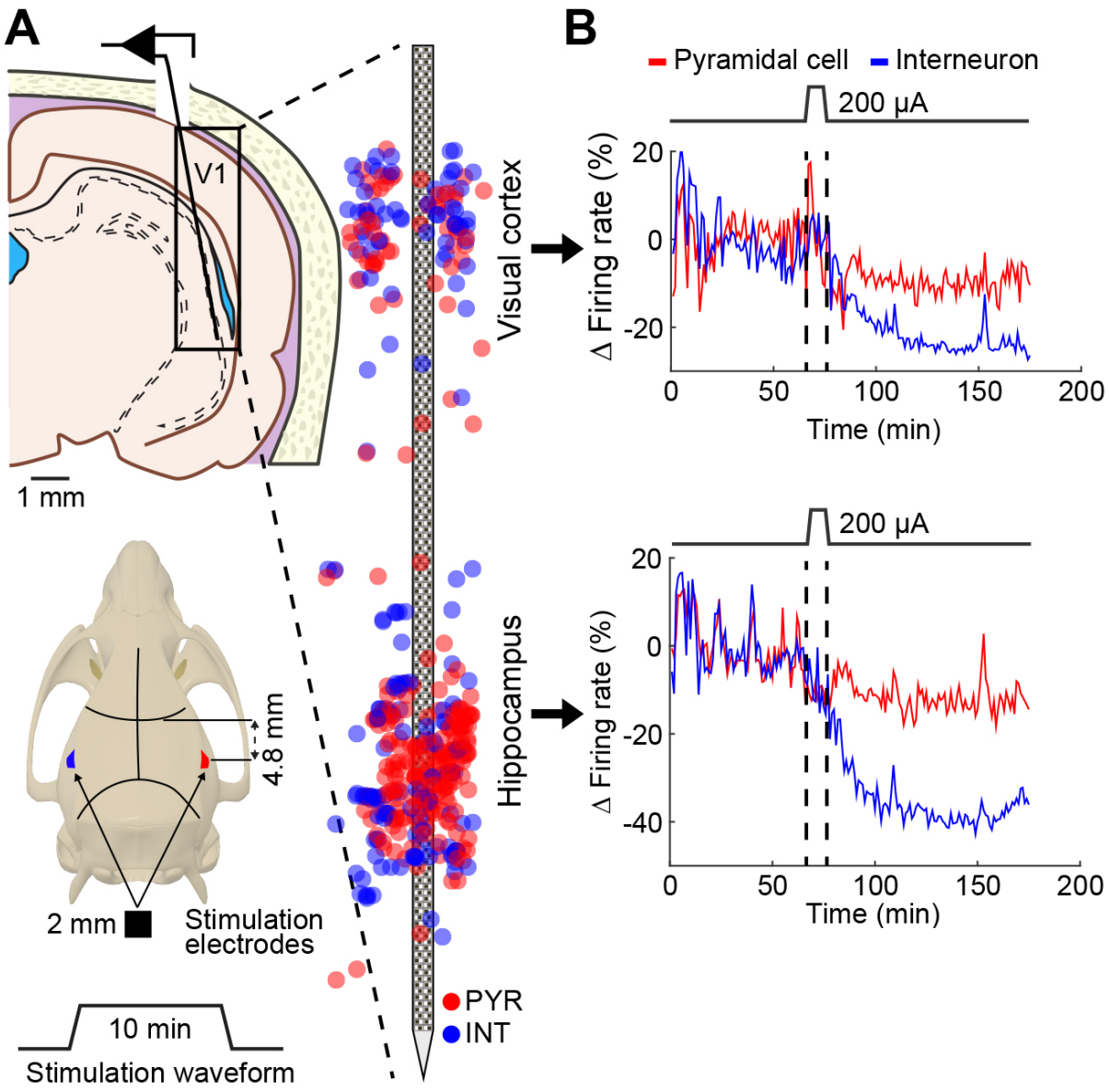
Target area *depth, neurons' morphology*

- Hippocampus is parallel with E-field
- Visual cortex has variable orientations

Different brain regions

Voroslakos et. al., 2021, eLife; Ongoing work

tDCS-induced neuroplasticity in rats



ΔF - percent change in spiking between Pre and Stim, Post

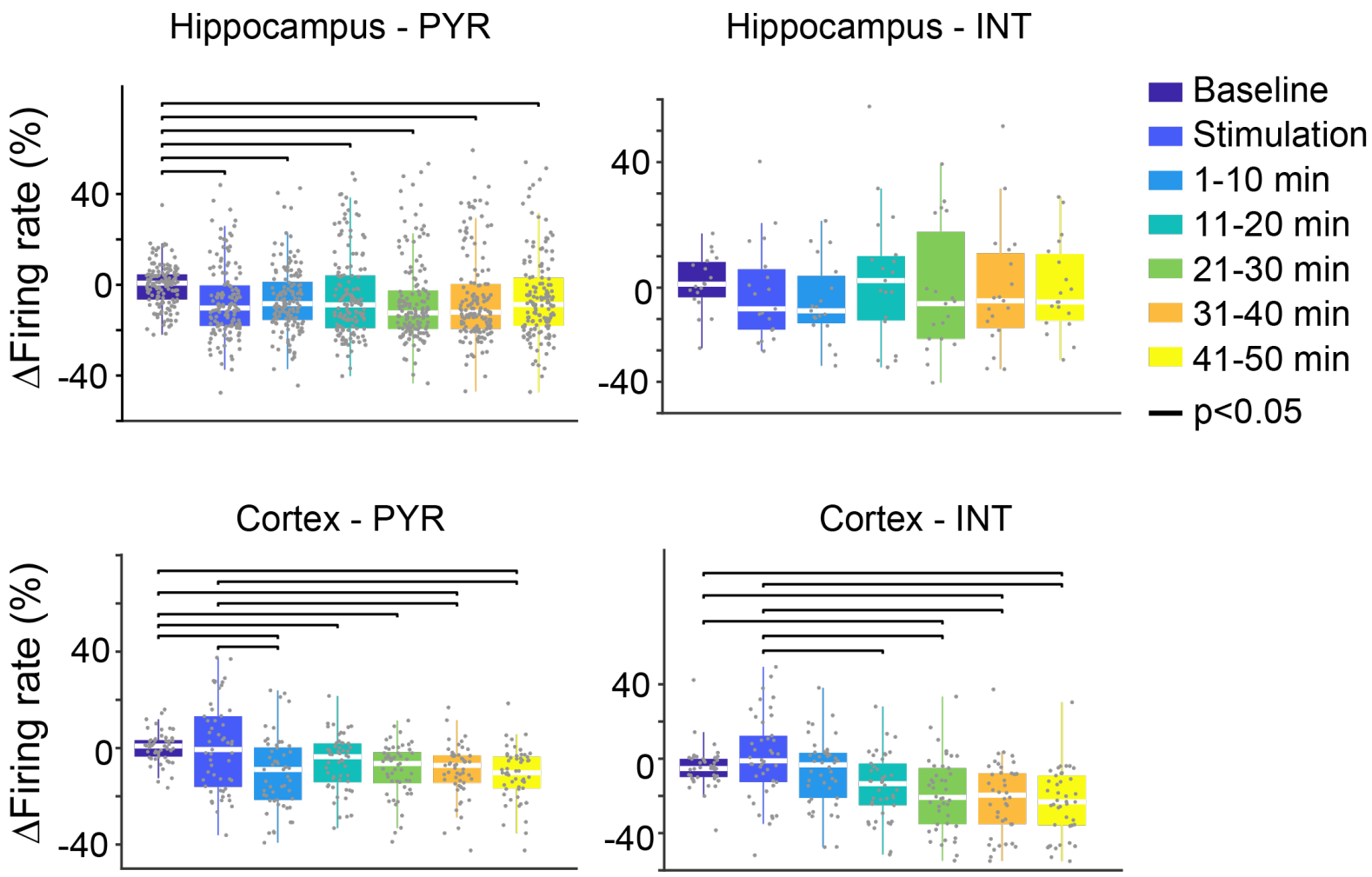
$$\Delta F = 100\ \frac{F_{stim} - Fpr_e}{\max(Fpr_e, Fs_{tim})}$$

tDCS-induced neuroplasticity in rats

n = 2 rats

Hippocampus
- 145 PYR and 19 INT

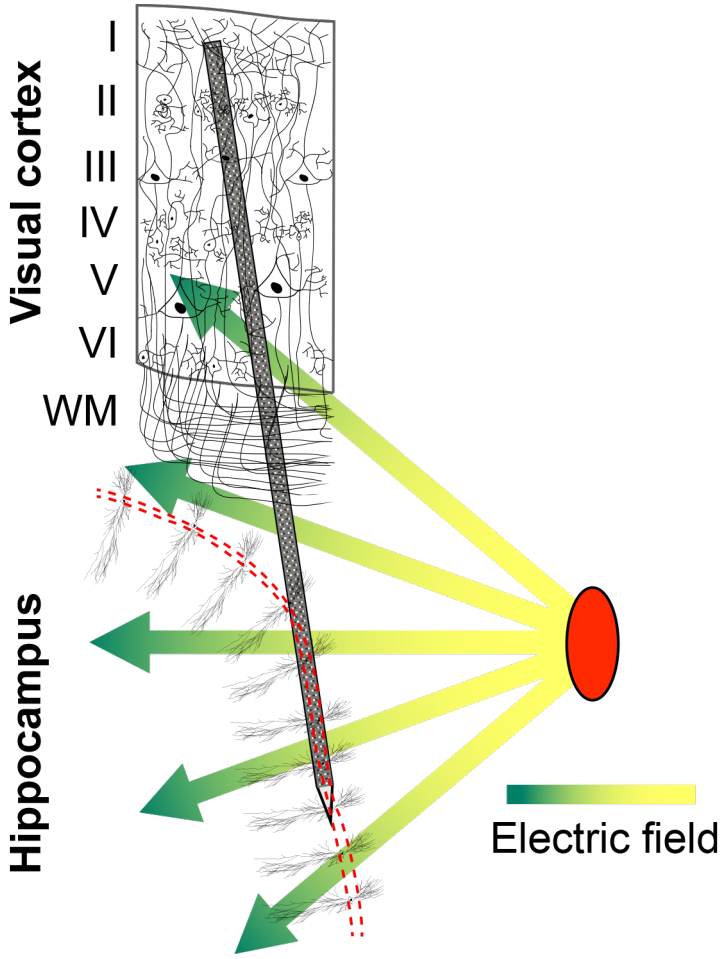
Cortex
- 53 PYR and 42 INT

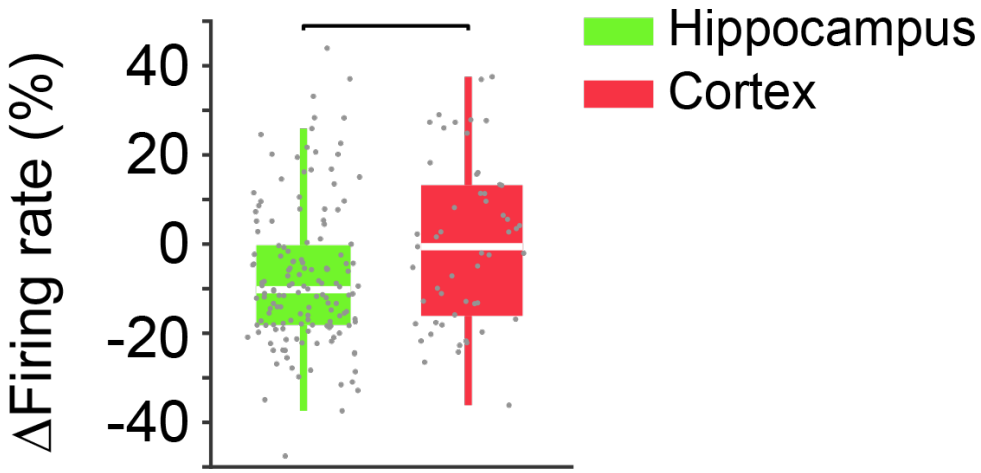


Large-scale recordings
- 384 channels @ 30 kS/s
- 80 Gb data/hour

tDCS-induced change in firing rate lasts 50 minutes

Neuronal response during tDCS





Hippocampus is more influenced by tDCS

- Better aligned to electric field
- Higher electric field in hippocampus

BUT visual cortex is also affected

Summary

1. We established a tDCS protocol in rats that can mimic human intensities.
    - Provide mechanistic explanations for findings in humans.
    - Optimization of stimulation protocols.
    - More thorough understanding of tDCS effects (e.g., state-dependent changes).

2. tDCS could induce neuroplasticity that outlasted the stimulation.

3. tDCS affected multiple brain regions, including hippocampus and visual cortex.


Arkells

Summary

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    - Provide mechanistic explanations for findings in humans.
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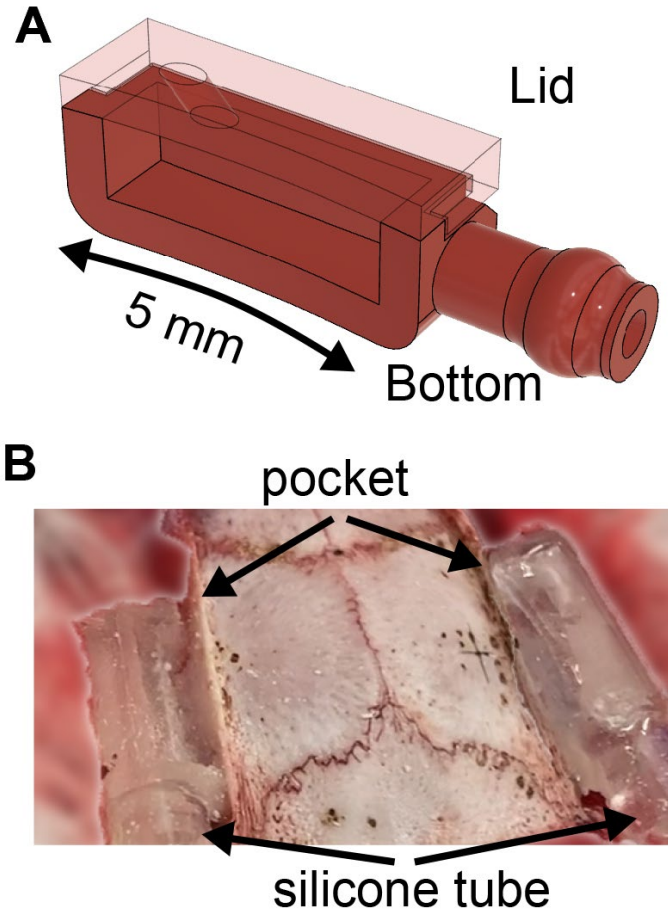
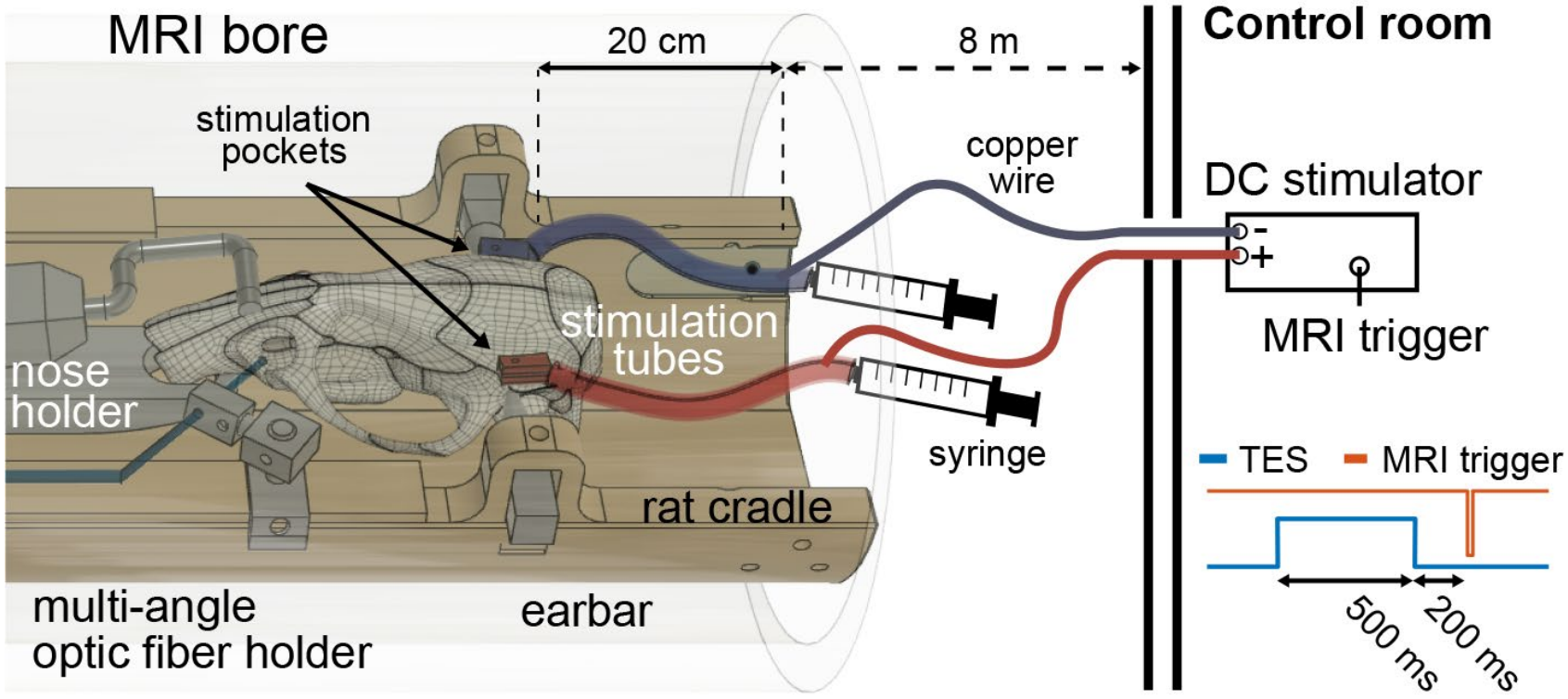
2. tDCS could induce neuroplasticity that outlasted the stimulation.

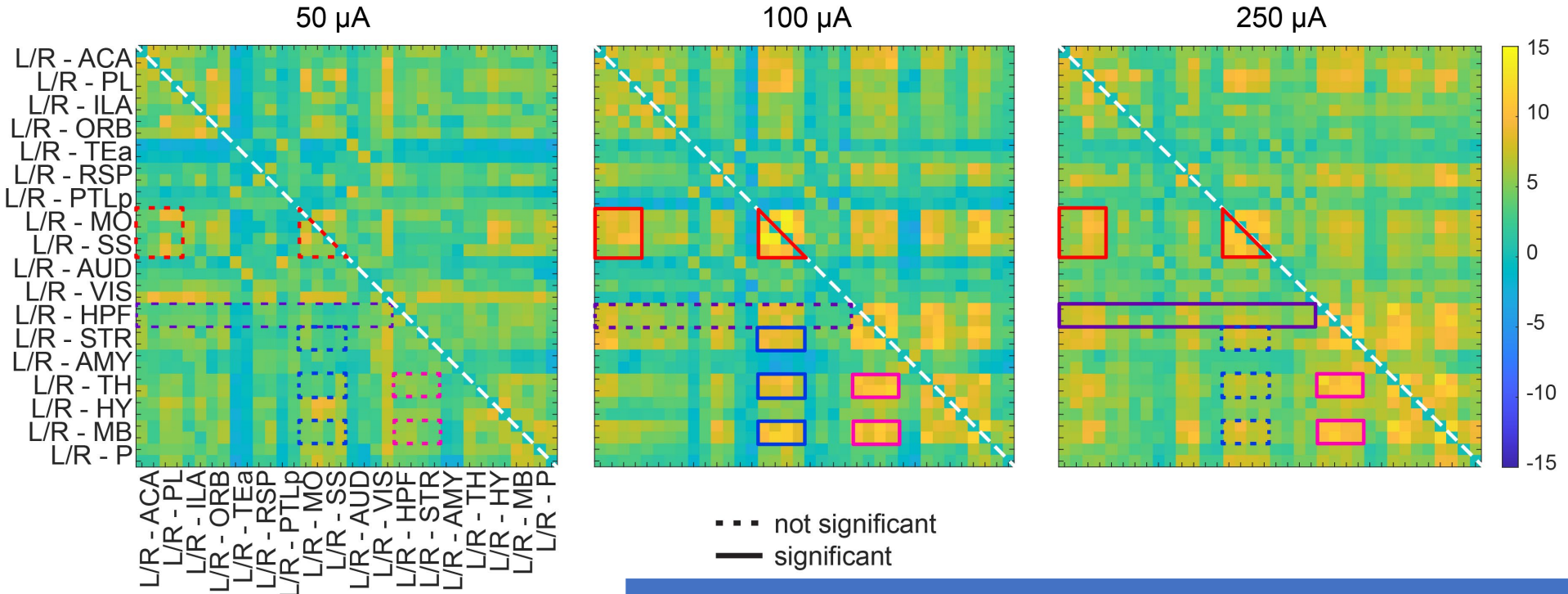
3. tDCS affected multiple brain regions, including hippocampus and visual cortex.

Combined neurostimulation and neuroimaging





TES-dose dependent BOLD activation pattern



MODULATED BRAIN NETWORKS		
50 µA	**100 µA**	**250 µA**
-	Somato-motor	Somato-motor
-	Somato-motor-prefrontal	Somato-motor-prefrontal
-	-	Cortico-hippocampal
-	Hippocampal-striatal-thalamic/midbrain	Hippocampal-striatal-thalamic/midbrain
-	Somato-motor-striatal/thalamic/midbrain	-