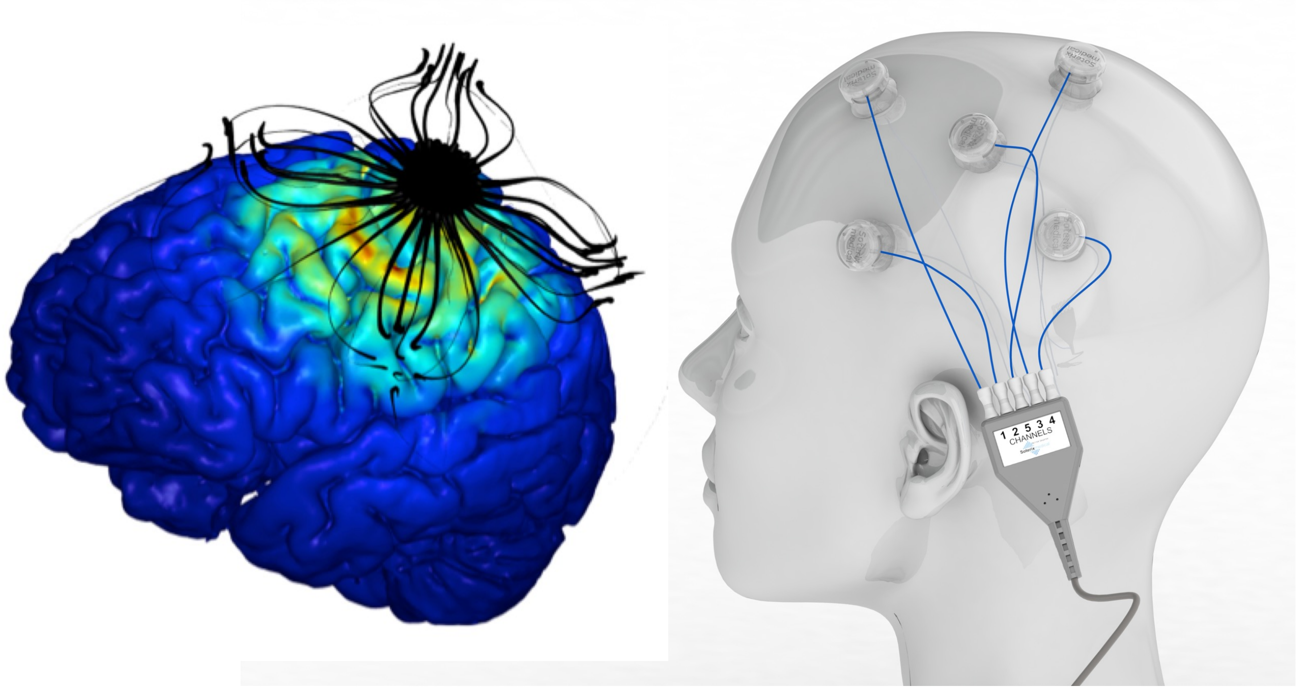
Design of non-invasive electrical brain stimulation

Marom Bikson, **The City College of New York**



Adantchede Louis Zannou, Mojtaba Belali Koochesfahani, Mahima Sharma. Lucas Parra, Marc Russo, Greg Kronberg, Abhishek Datta, Niranjan Khadka, Zeinab Esmaeilpour, Belen Lafon, Mohamad FallahRad, Mark Jackson, Tianhe Zhang, Rosana Esteller, Asif Rahman, Darpan Chakraborty Dennis Truong, Hanoch Kaphzan, Vividha Bhaskar, Thomas Radman

NJIT, April 19. 2024

I will like to explain how transcranial electrical brain stimulation works,

but more then that, I want to show how biomedical engineering thinking drives innovation.

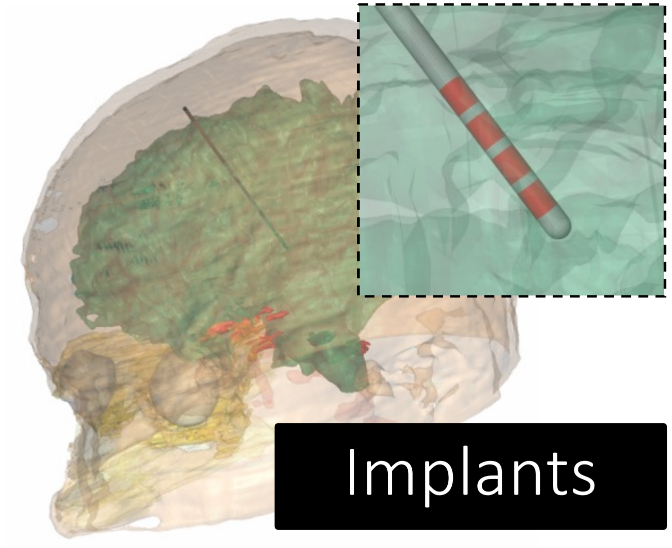
I will not talk about uses of brain stimulation (like treatment of pain, depression, dementias, or brain enhancement) but welcome questions.

Disclosure

The City University of New York holds patents on brain stimulation with MB as inventor. MB has equity in Soterix Medical Inc. MB consults, received grants, assigned inventions, and/or served on the SAB of SafeToddles, Boston Scientific, GlaxoSmithKline, Biovisics, Mecta, Lumenis, Halo Neuroscience, Google-X, i-Lumen, Humm, Allergan (Abbvie), Apple, Ybrain, Ceragem, Remz. MB is supported by grants from Harold Shames and the National Institutes of Health: NIH-NIDA UG3DA048502, NIH-NIGMS T34 GM137858, NIH-NINDS R01 NS112996, NIH-NINDS R01 NS101362, and NIH-G-RISE T32GM136499.

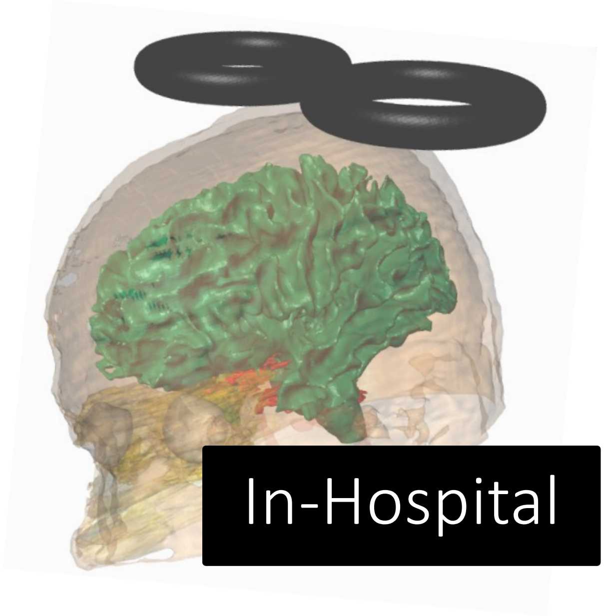
Slides and References
@MaromBikson

What defines neuromodulation technologies is how energy is delivered to what target



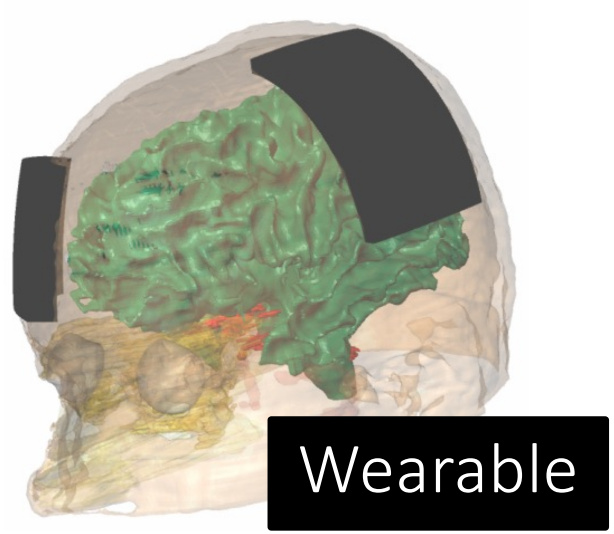
Deep Brain Stimulation (DBS)

Spinal Cord Stimulation (SCS)



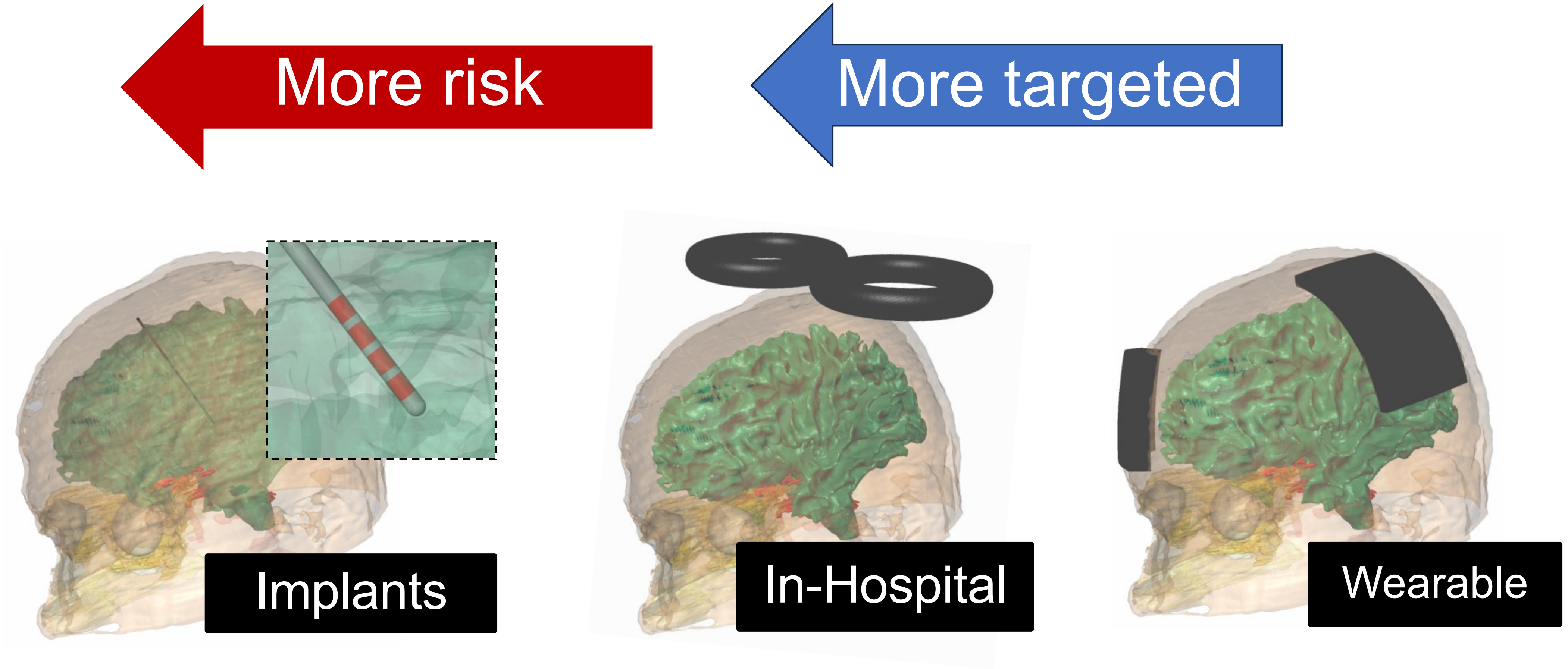
Transcranial Magnetic Stimulation (TMS)

Electroconvulsive Therapy



Transcranial Electrical Stimulation (tES)

Transcranial Direct Current Stimulation (tDCS)



Deep Brain Stimulation (DBS)

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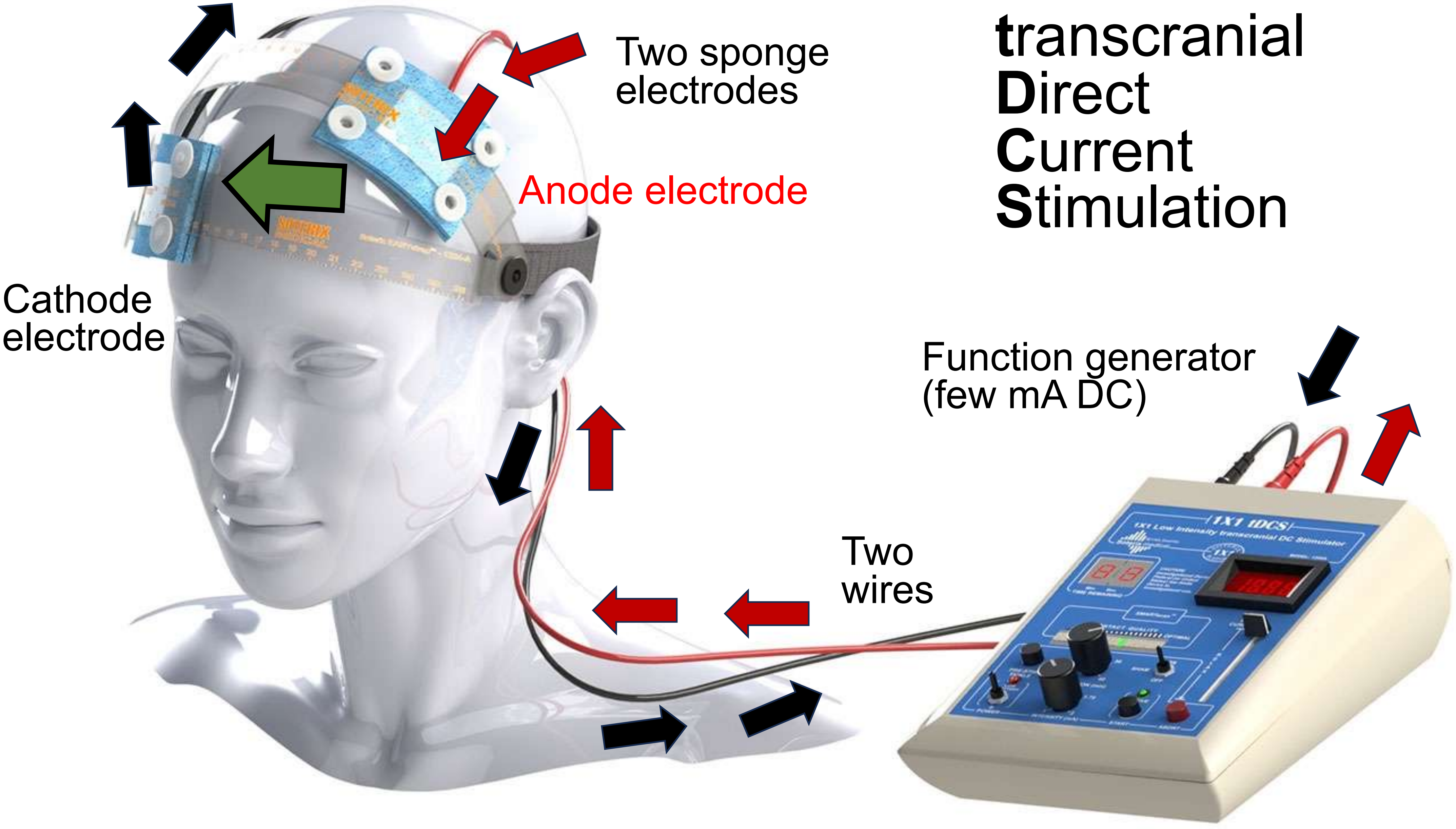
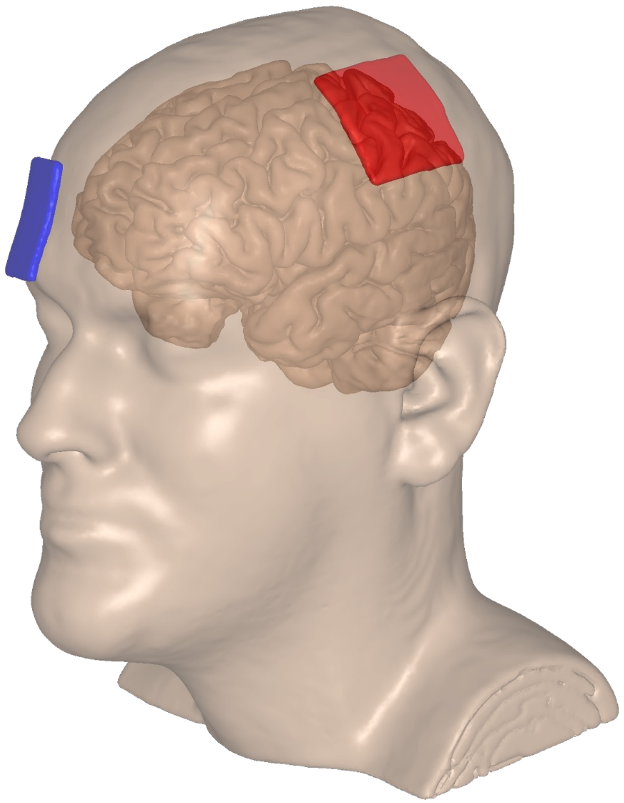

transcranial
Direct
Current
Stimulation
Two sponge electrodes
Anode electrode
Cathode electrode
Function generator (few mA DC)
Two wires
1X1 tDCS

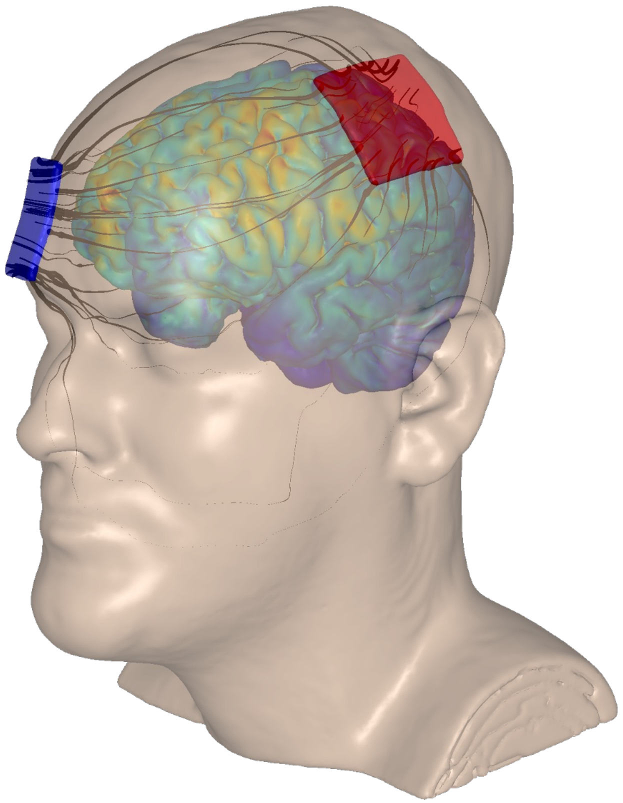
Conventional tDCS



Simulation of brain current flow

Datta et al. Gyri-precise head model of transcranial direct current stimulation: Improved spatial focality using a ring electrode versus conventional rectangular pad. *Brain Stimulation*. 2009

Conventional tDCS



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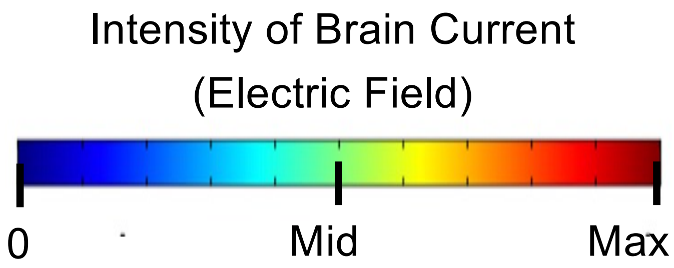

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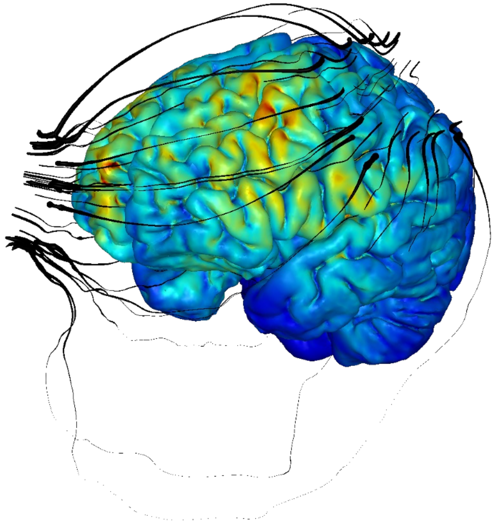

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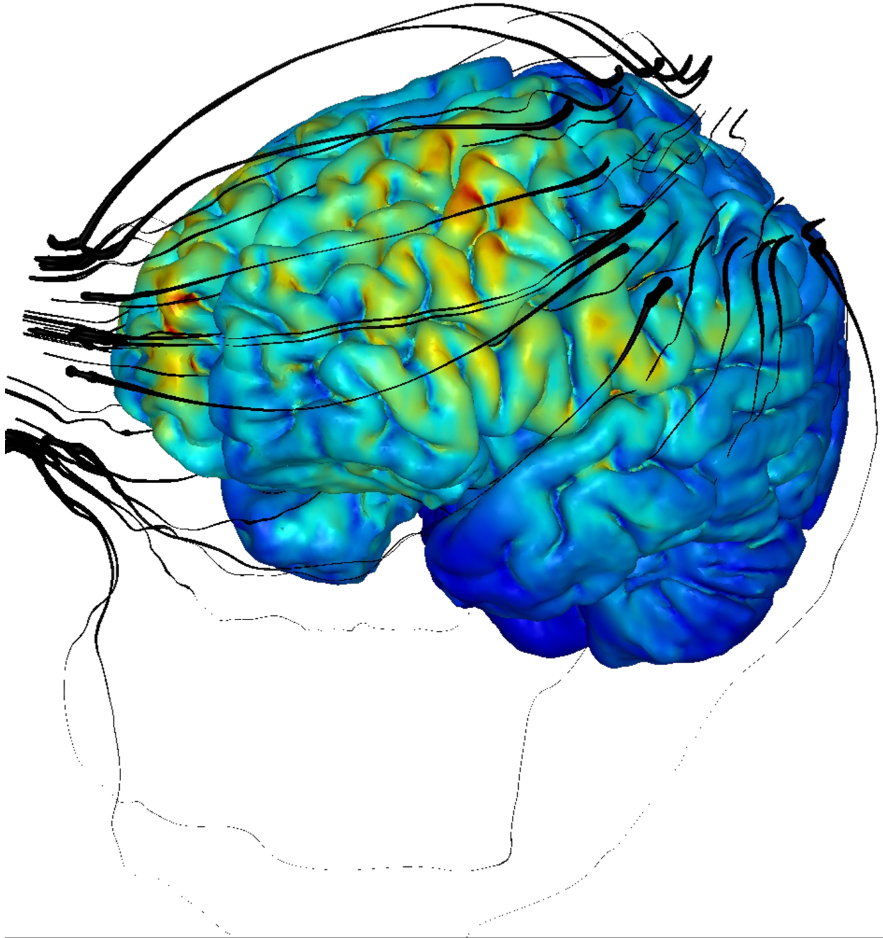

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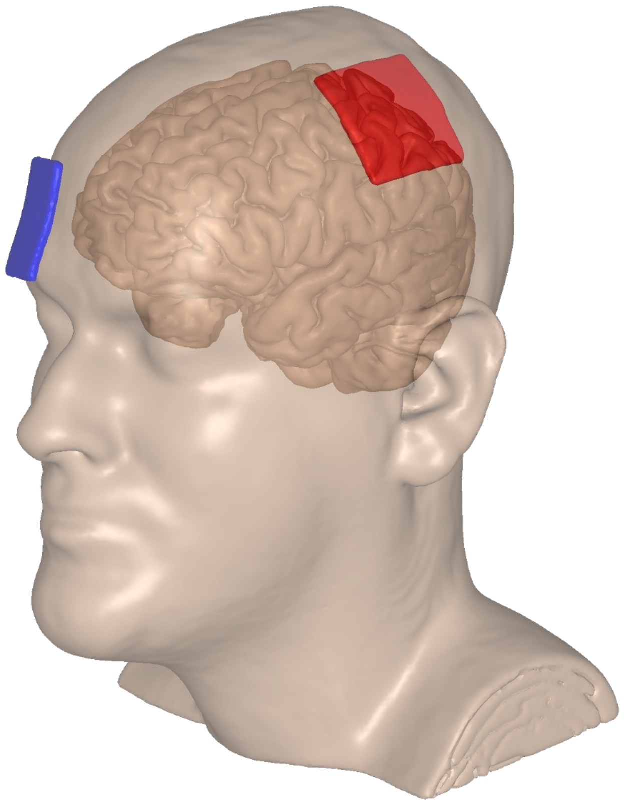

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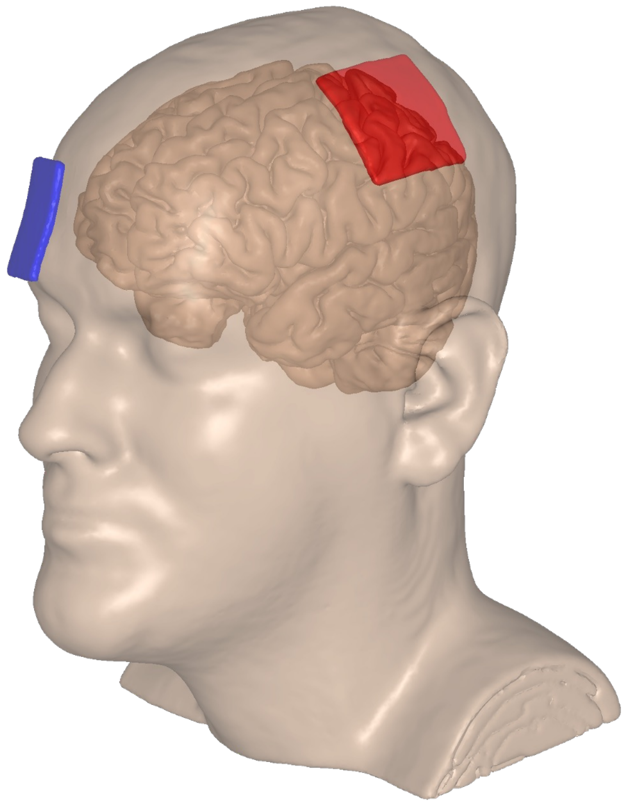
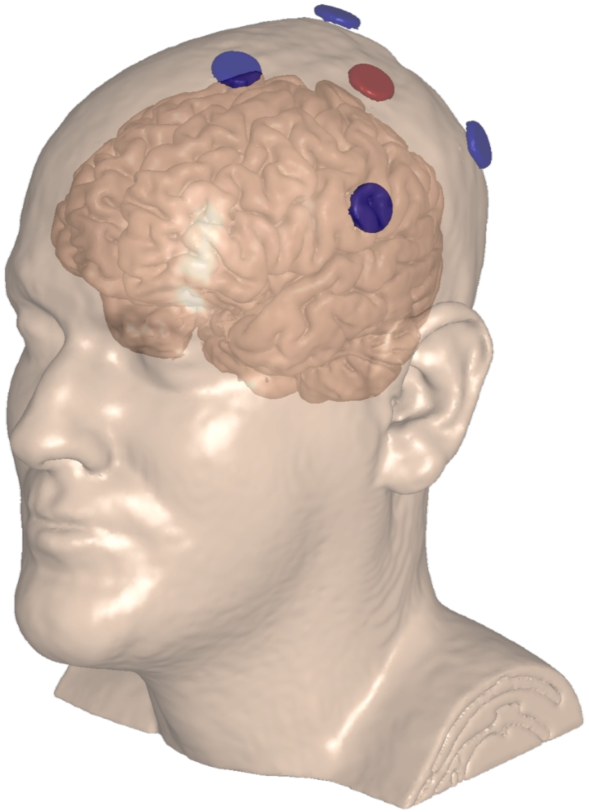
Conventional tDCS

High Definition tDCS





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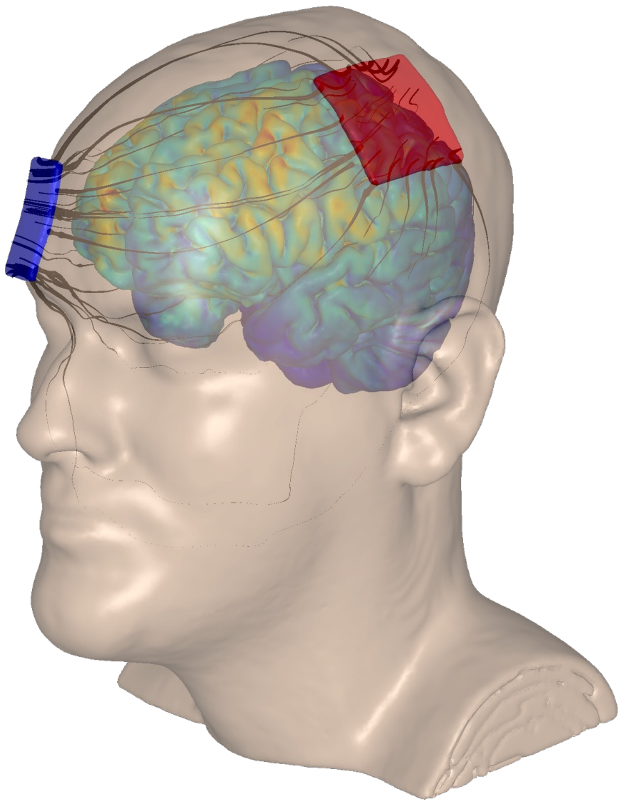
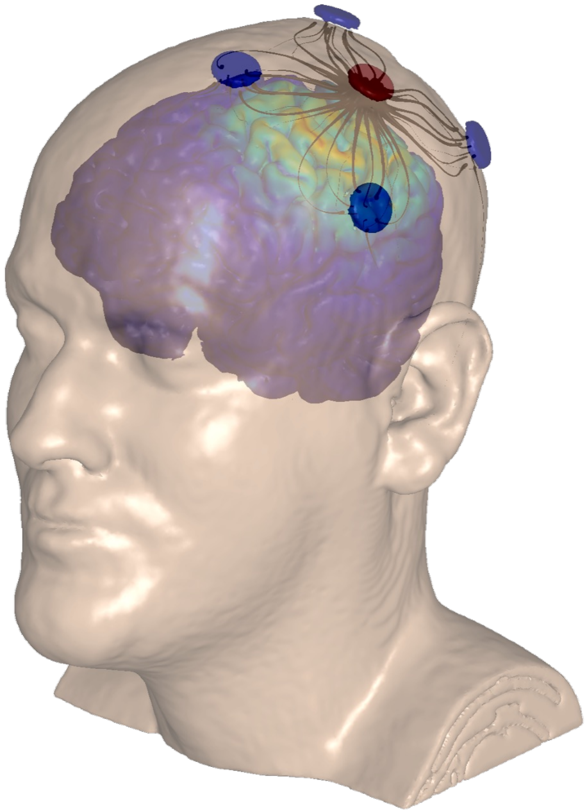


High Definition tDCS



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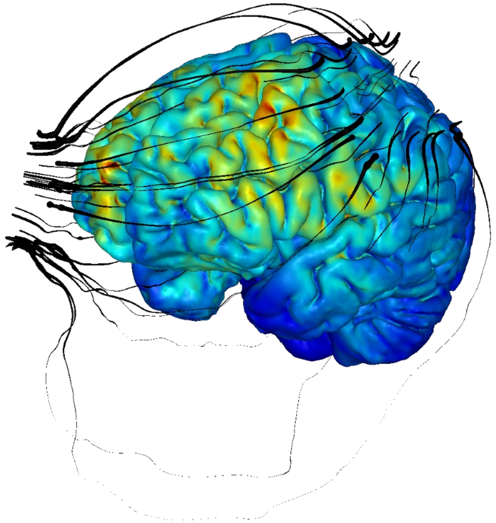

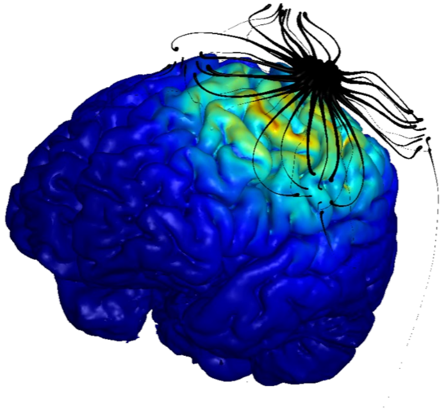

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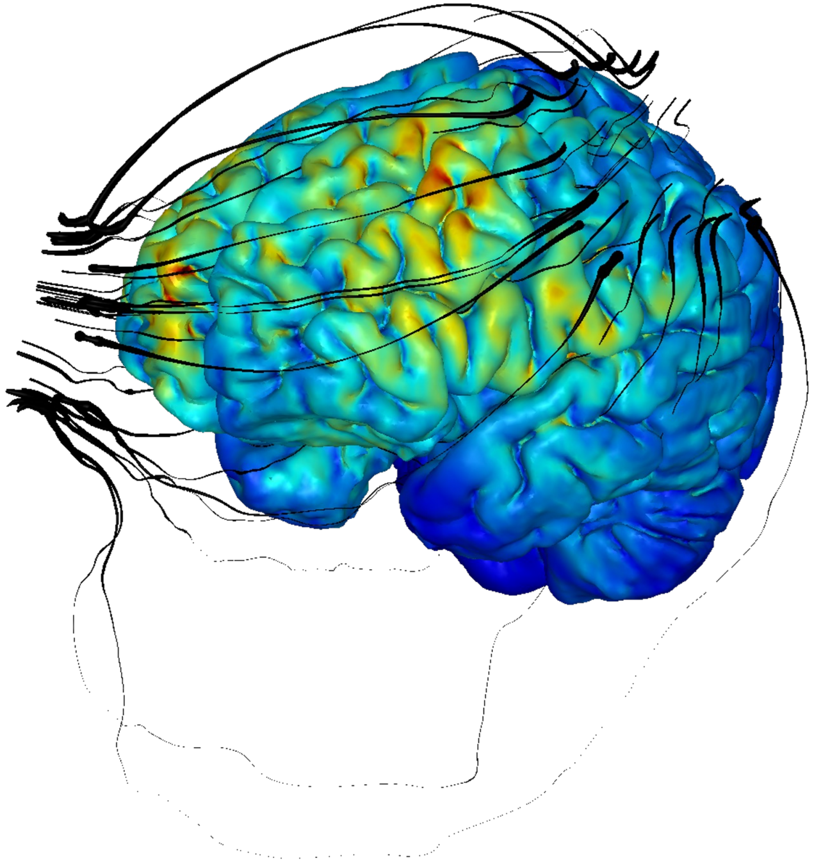
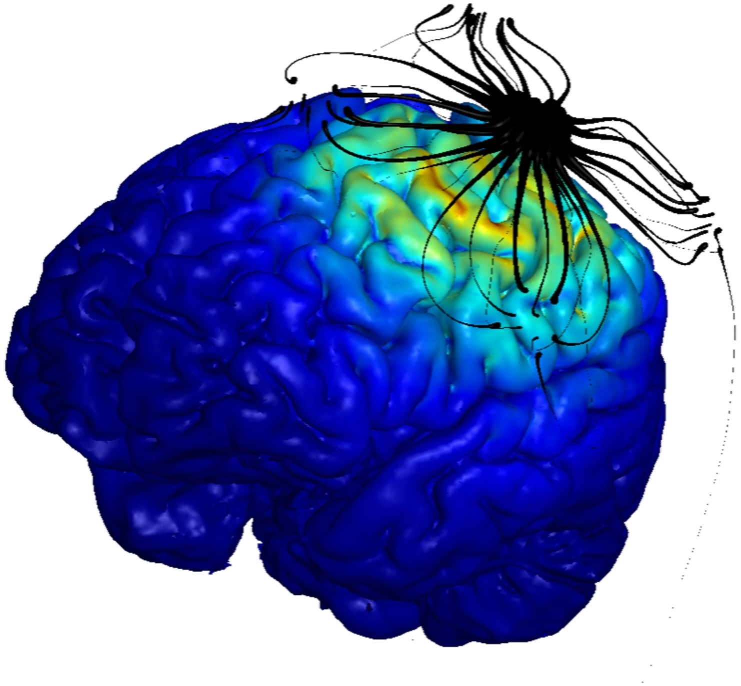


Simulation of brain current flow

High Definition tDCS



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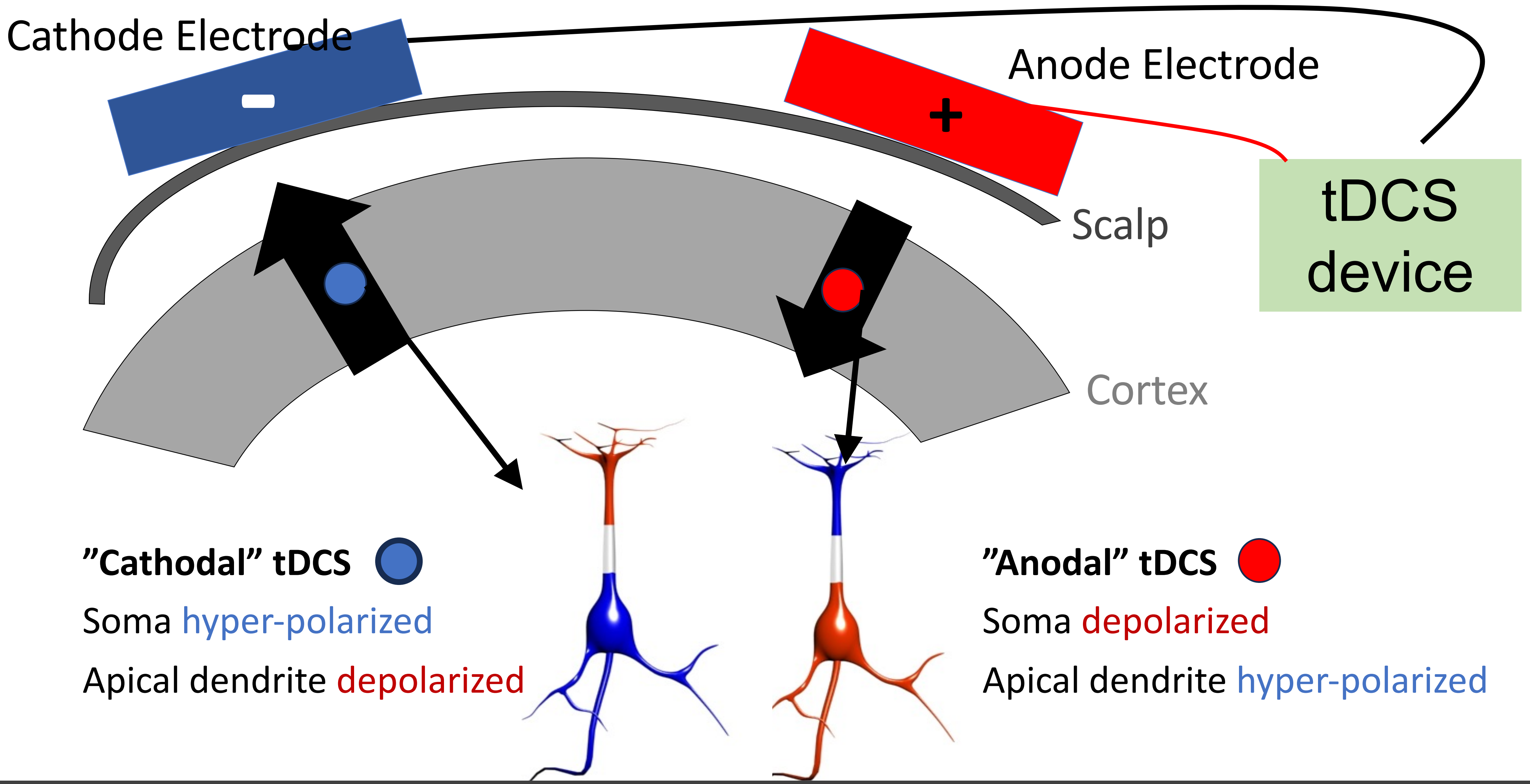
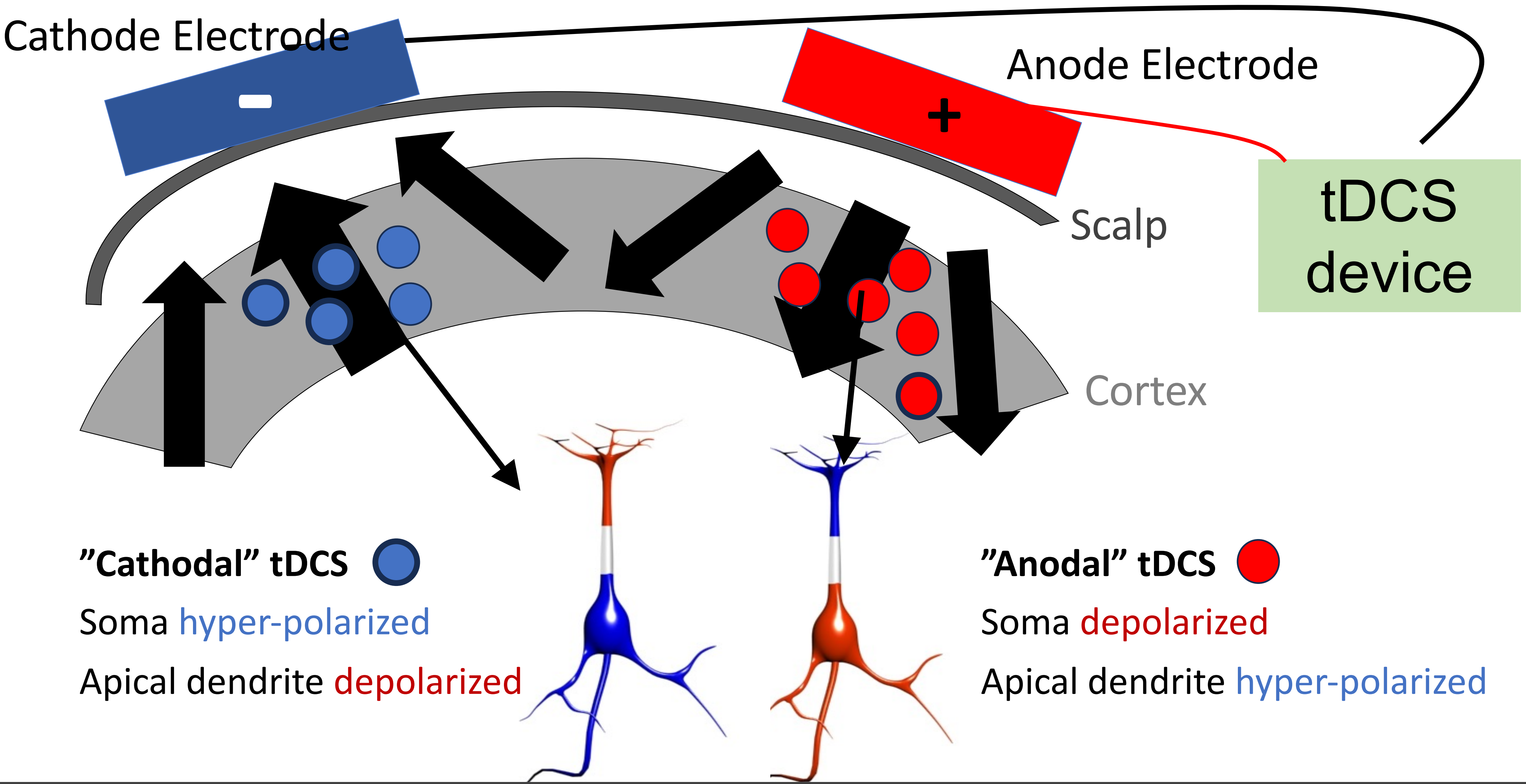


Radman et al. Role of cortical cell type and morphology in subthreshold and suprathreshold uniform electric field stimulation in vitro. . Brain Stimulation. 2009



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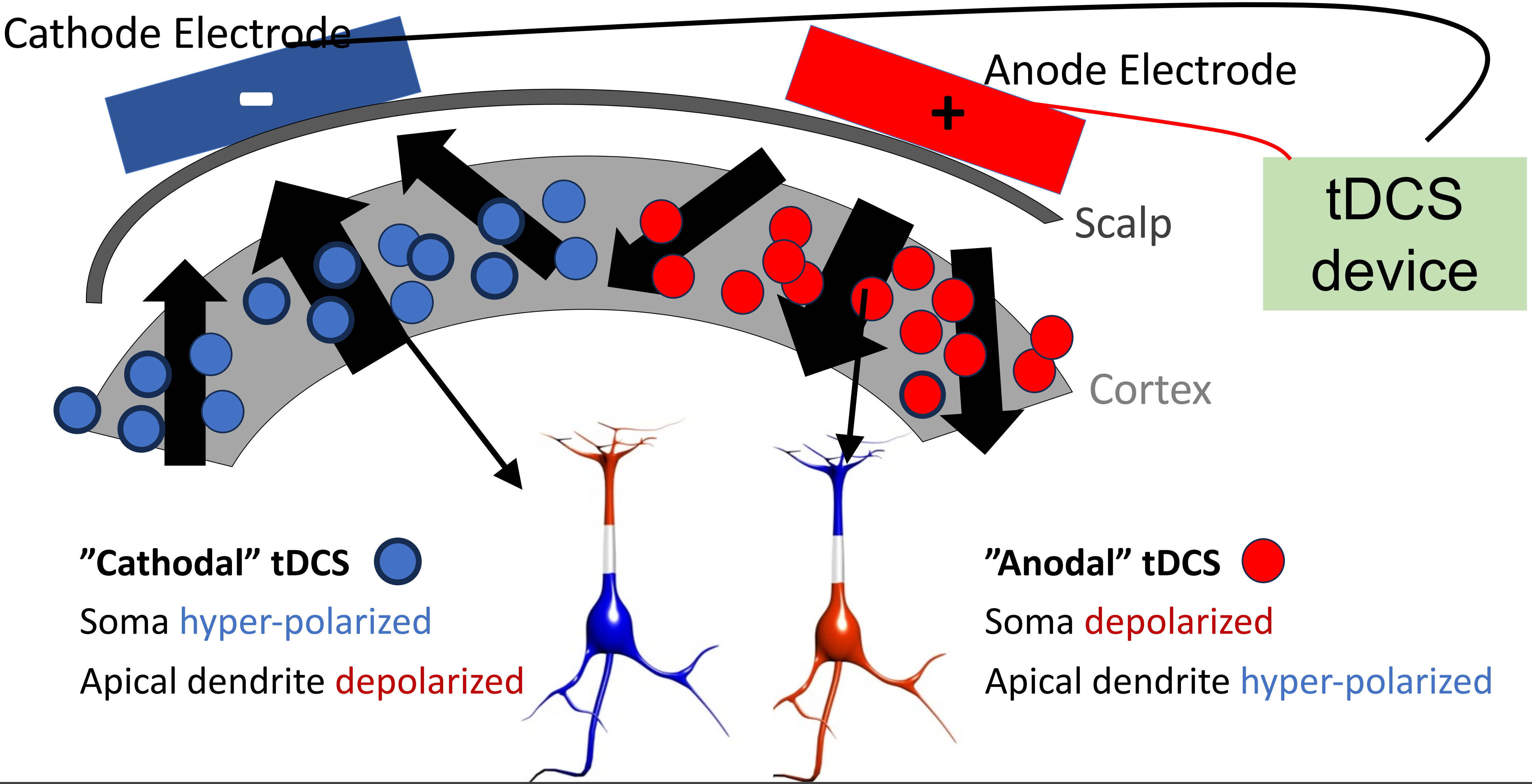

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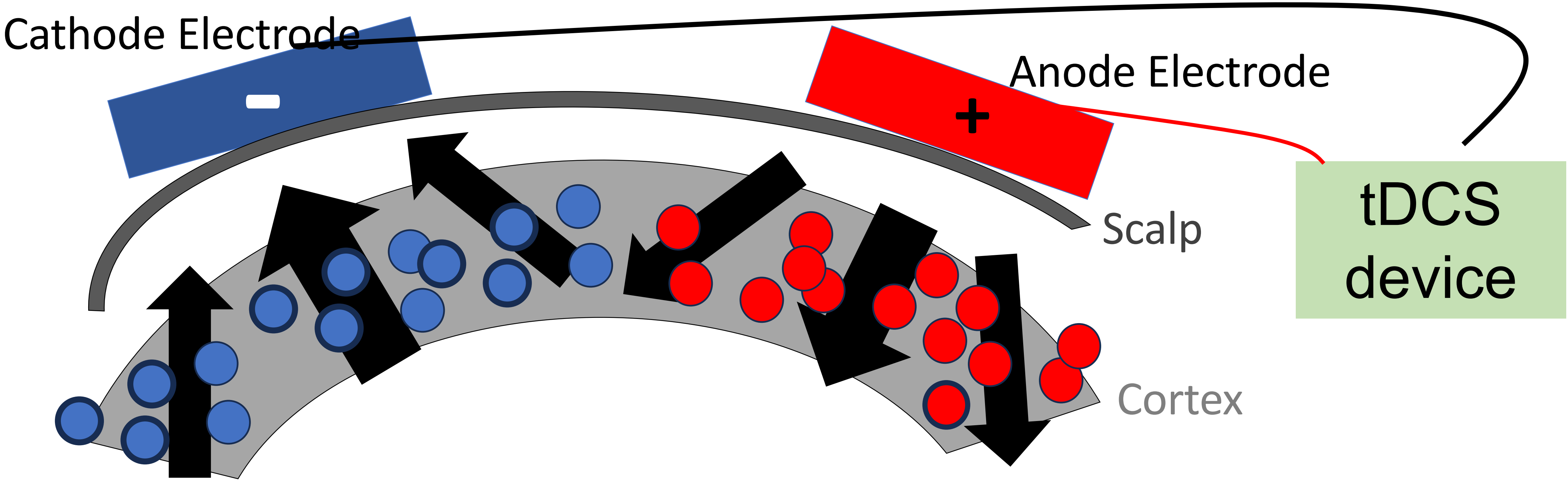
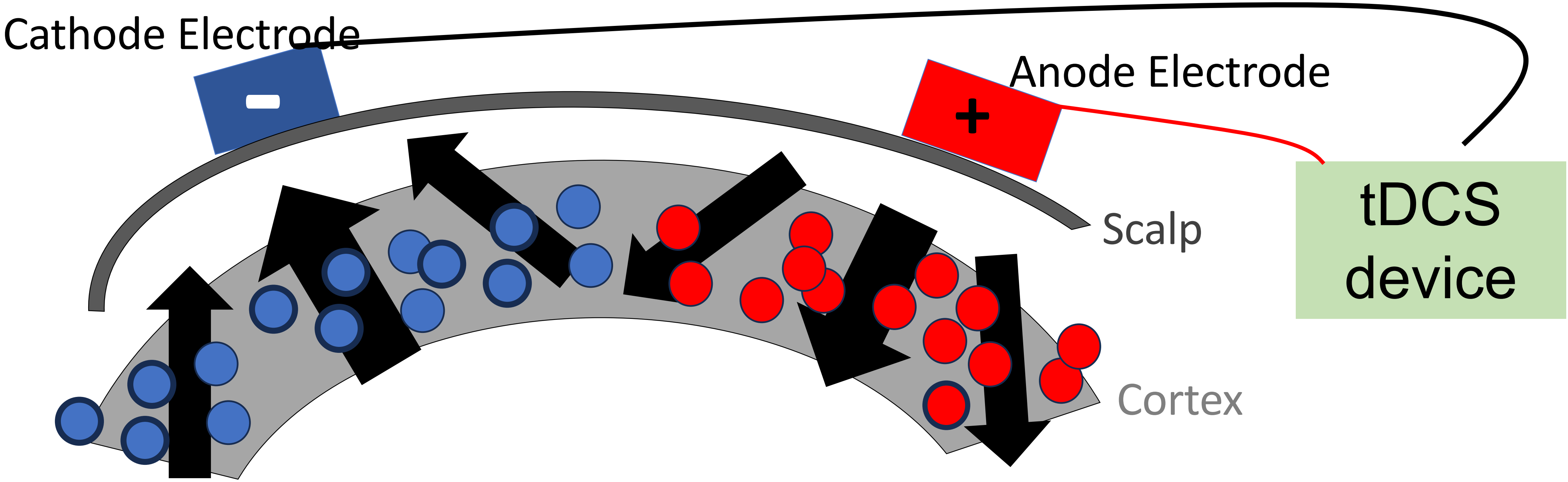
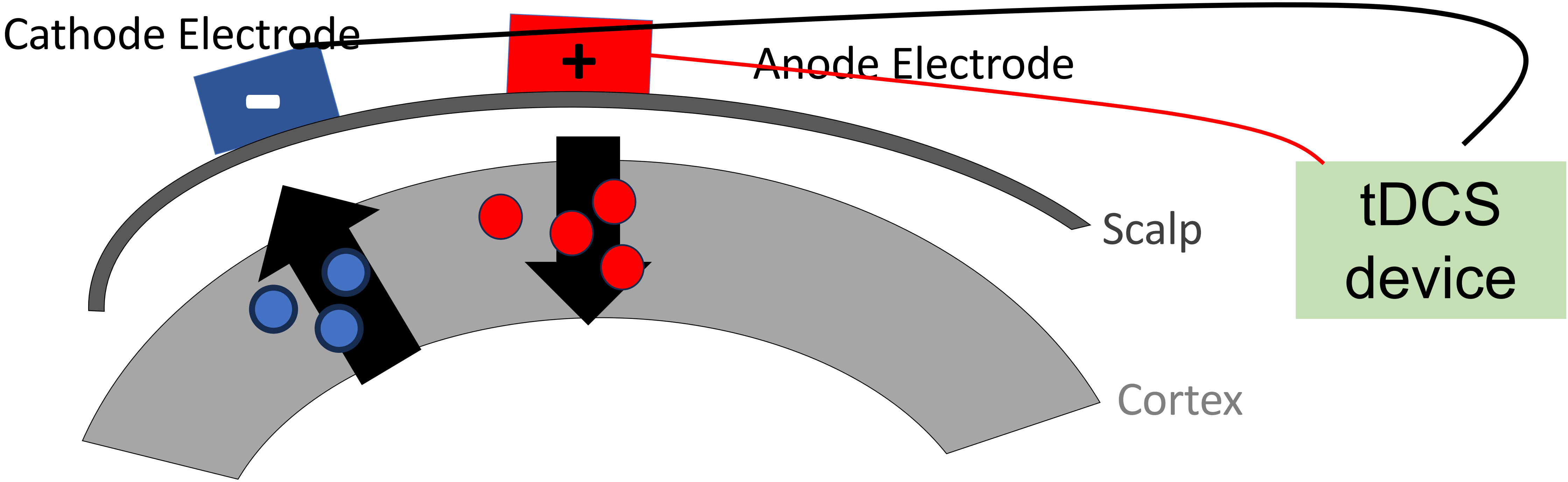


tDCS with two large electrodes leads to diffuse current flow and stimulation.



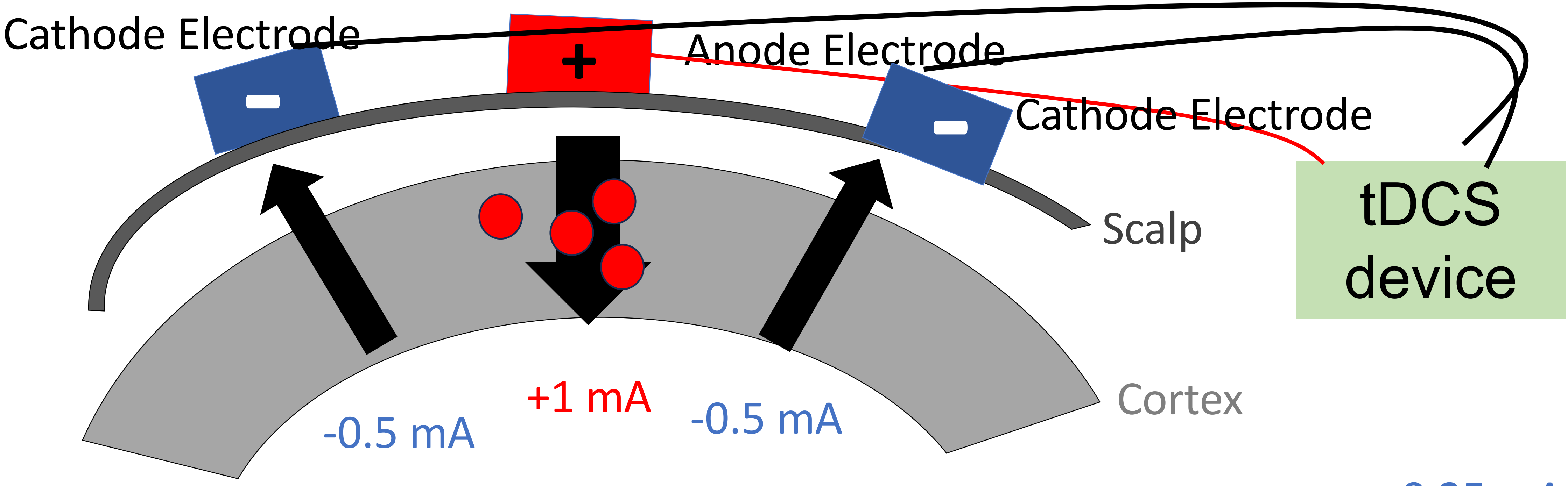
Smaller electrodes called “High Definition” (HD).

Making electrodes small does not in itself make stimulation focal. Current must still travel between electrodes.

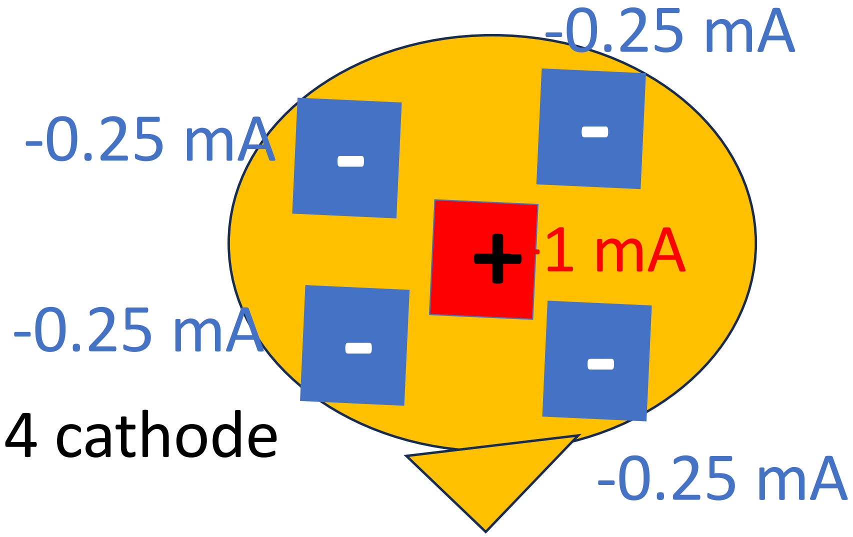


Make electrodes small (High Definition) and moving them closer together make current focal.

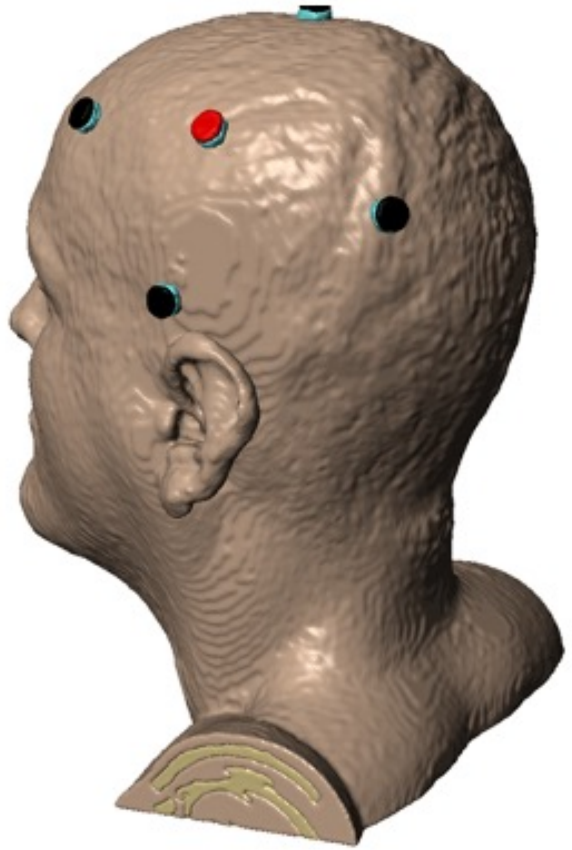
With two electrodes you have an anodal and cathodal regions.



Adding more “return” cathodes, makes the cathodal weaker. Leaving anodal strong.



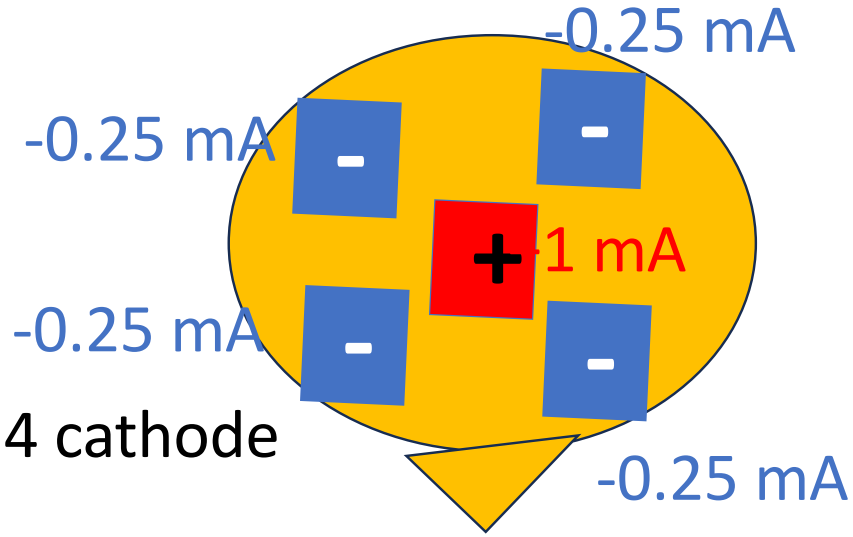
1 center anode x 4 cathode
4x1-HD-tDCS



Cathode Electrodes (-0.25 mA)

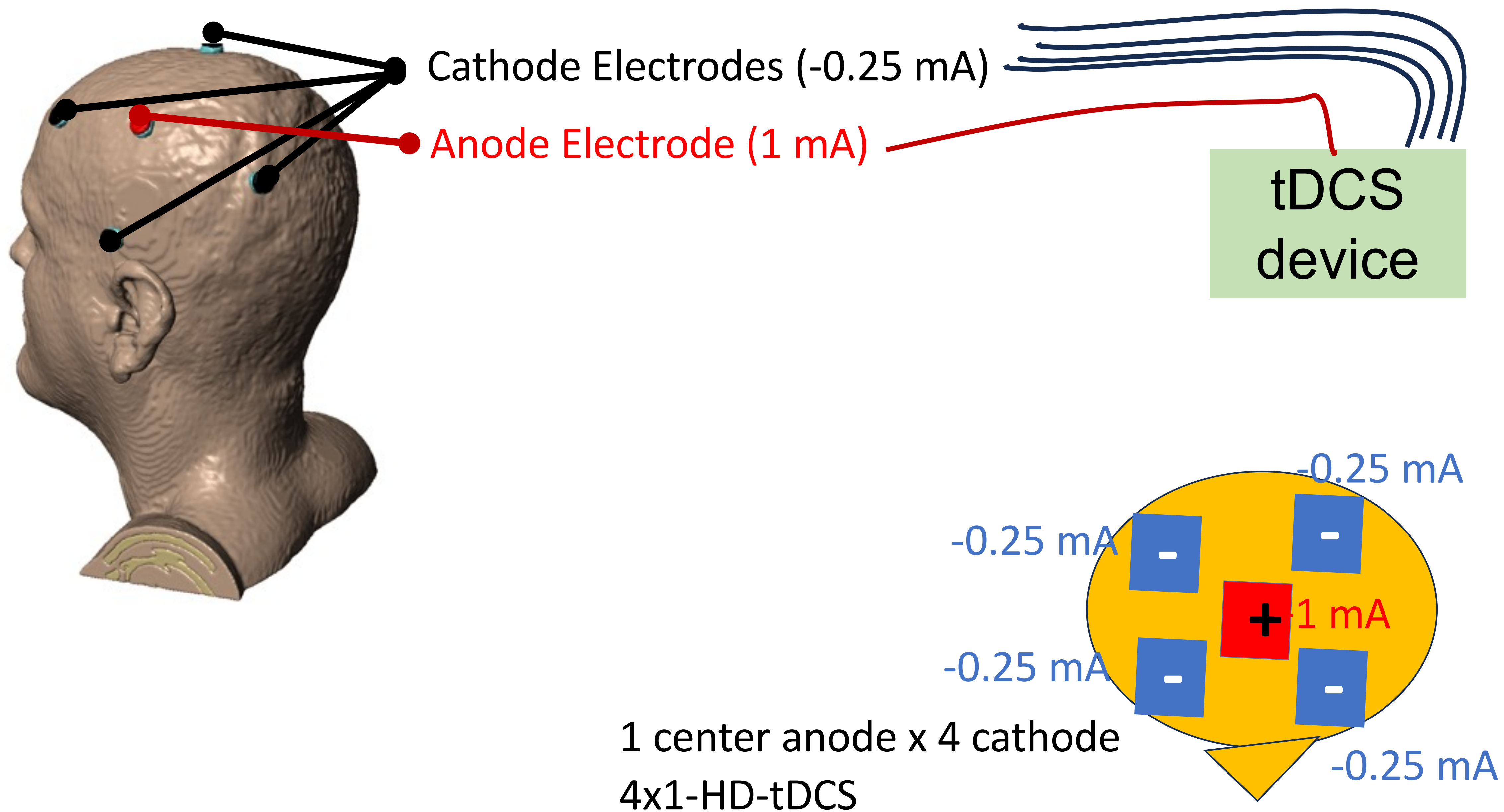
Anode Electrode (1 mA)

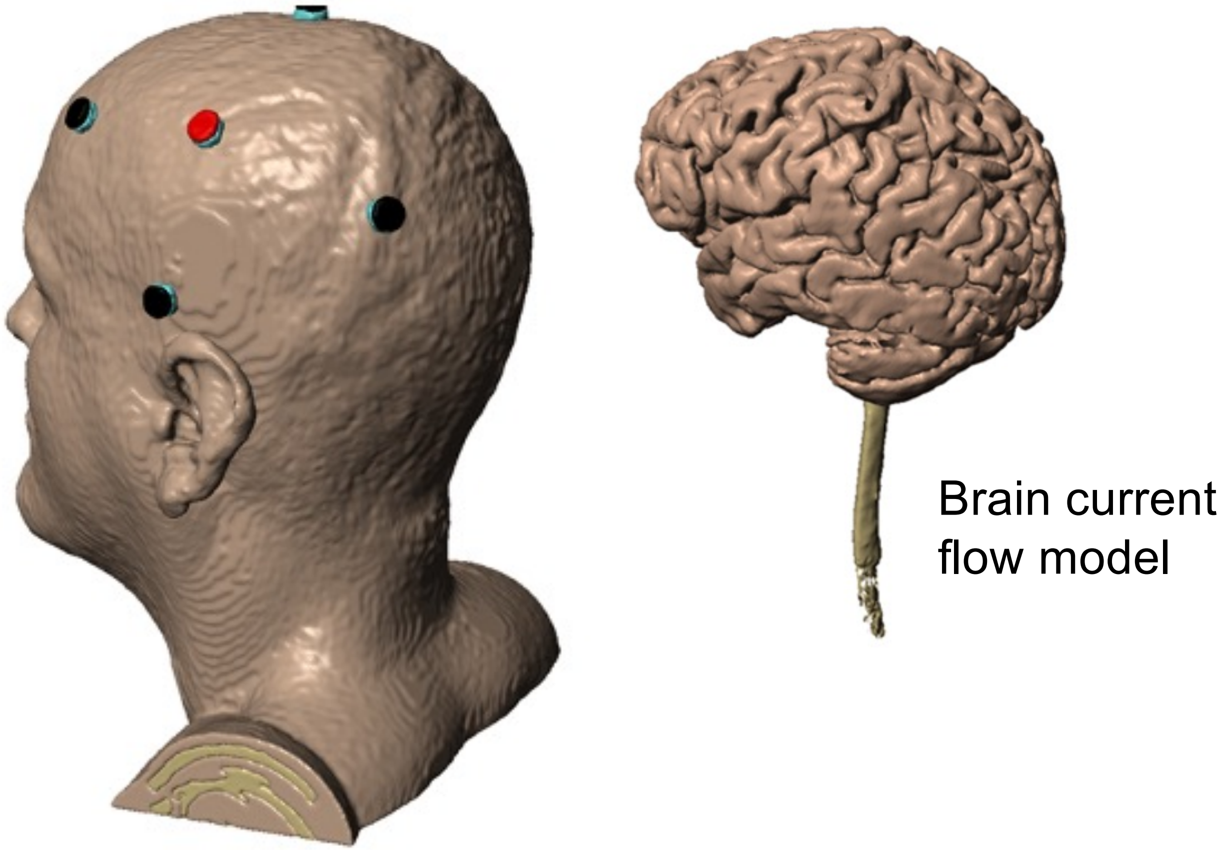
tDCS device

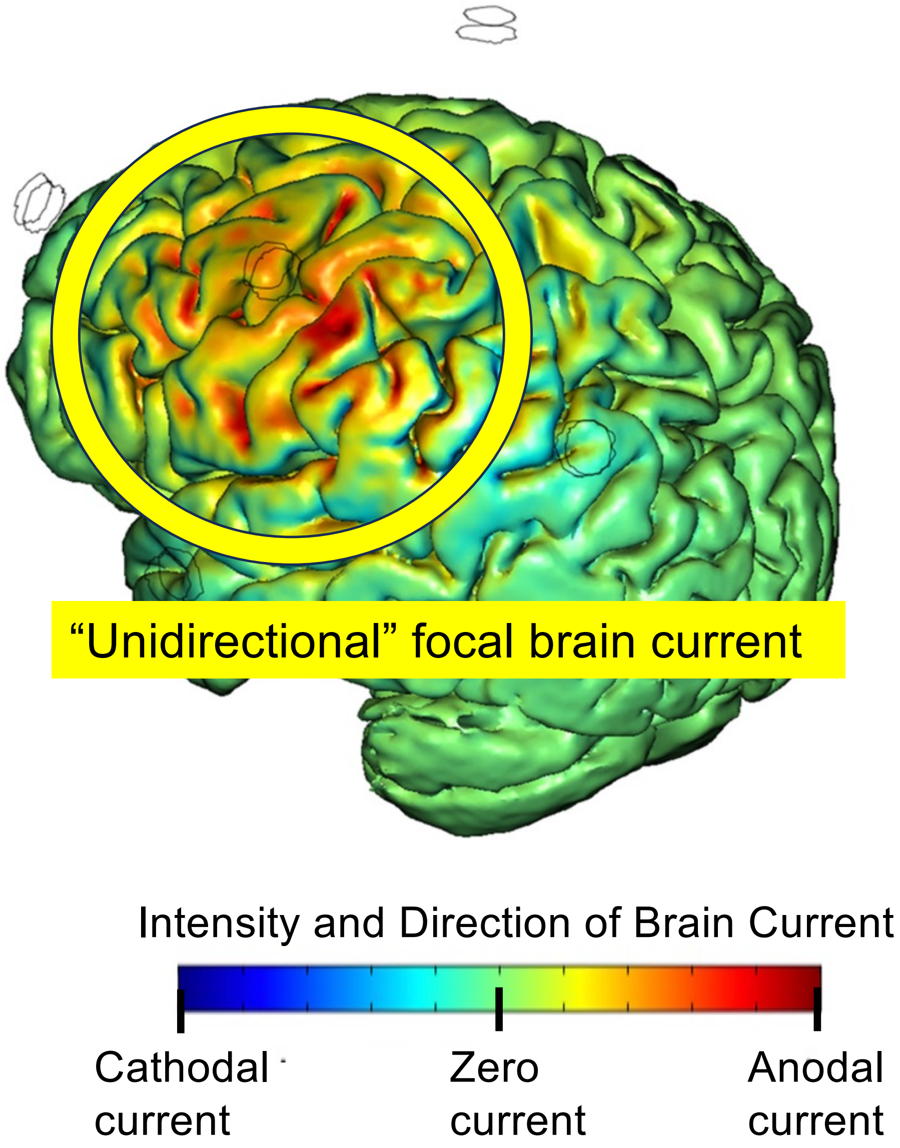


1 center anode x 4 cathode

4x1-HD-tDCS


Cathode Electrodes (-0.25 mA)
Anode Electrode (1 mA)
tDCS device
-0.25 mA
-0.25 mA
1 mA
-0.25 mA
-0.25 mA
1 center anode x 4 cathode
4x1-HD-tDCS

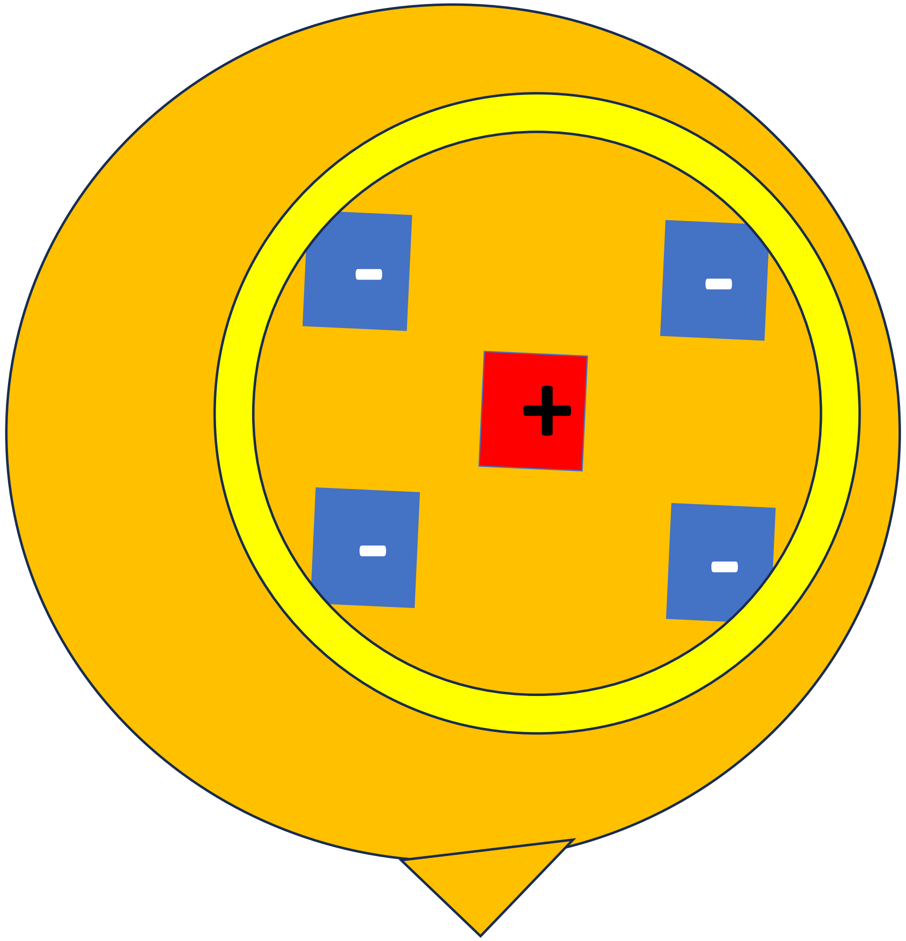




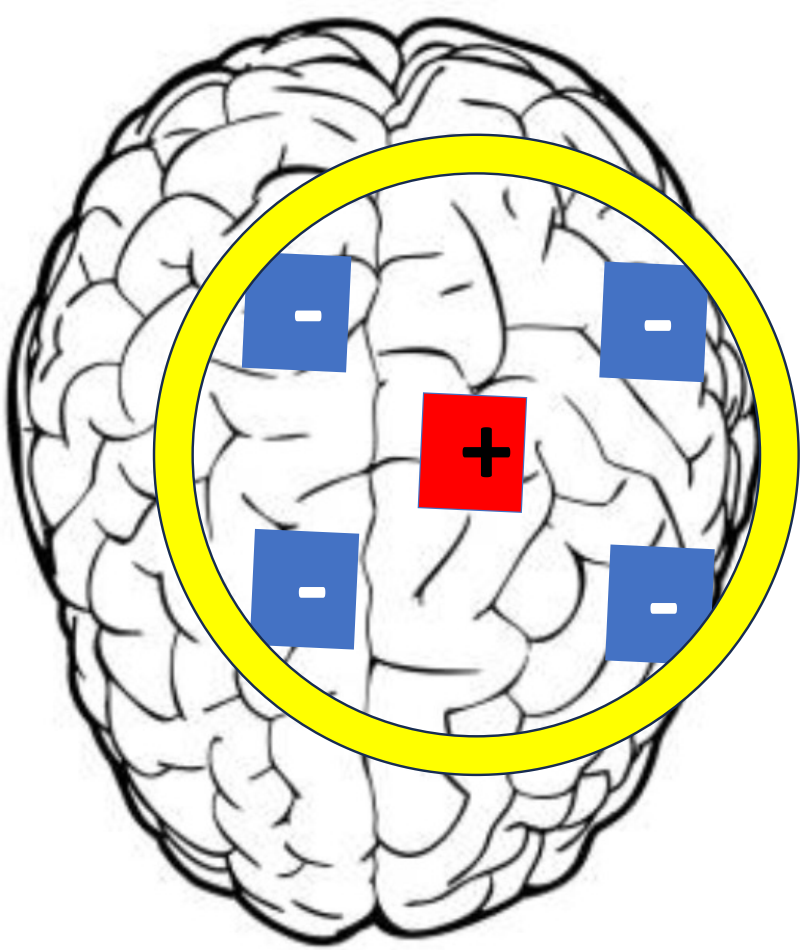
1 center anode x 4 cathode: 4x1-HD-tDCS

Cathode Electrodes (-0.25 mA) Anode Electrode (1 mA)

Villamar et al. Focal modulation of the primary motor cortex in fibromyalgia using 4×1-ring high-definition transcranial direct current stimulation (HD-tDCS). *Journal of Pain*, 2013



The outer electrodes form a ring.
The area of brain targeted is inside the ring.



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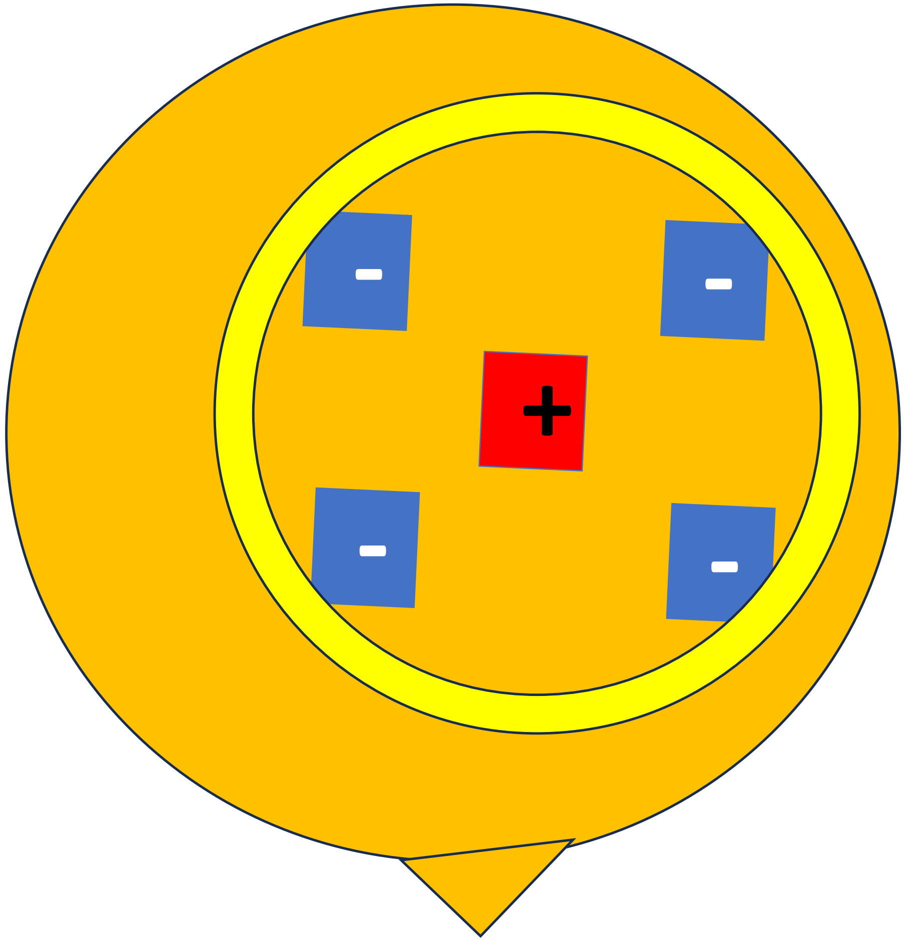

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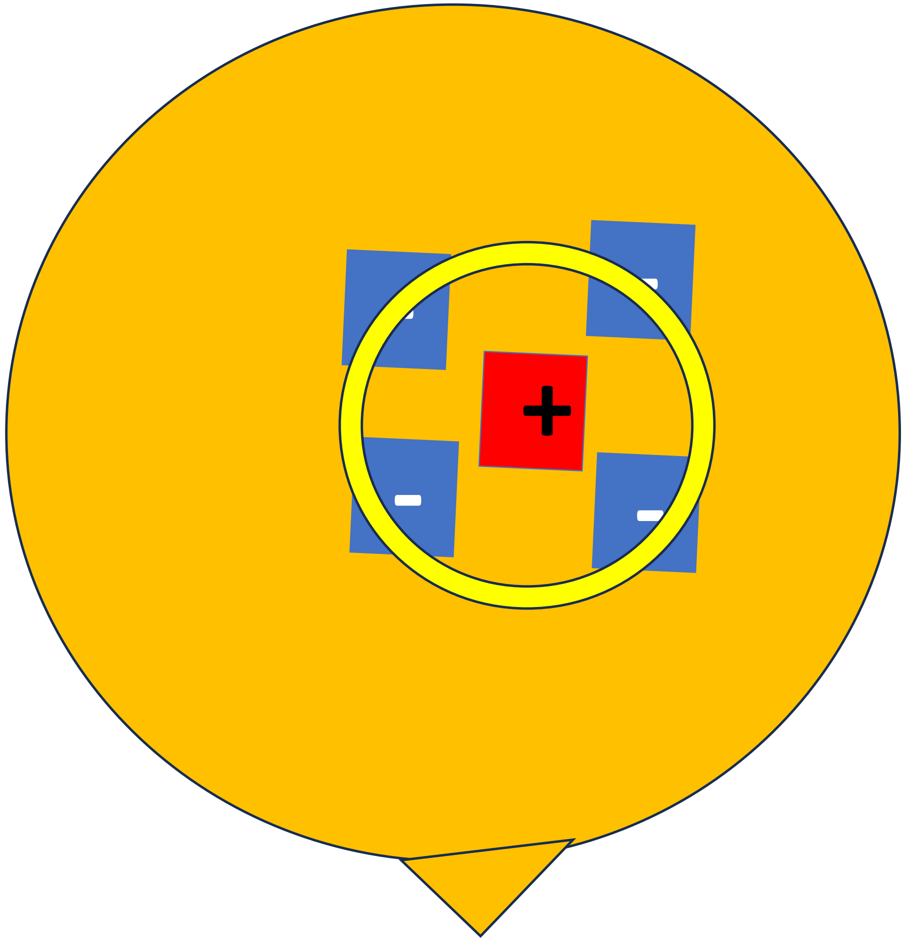
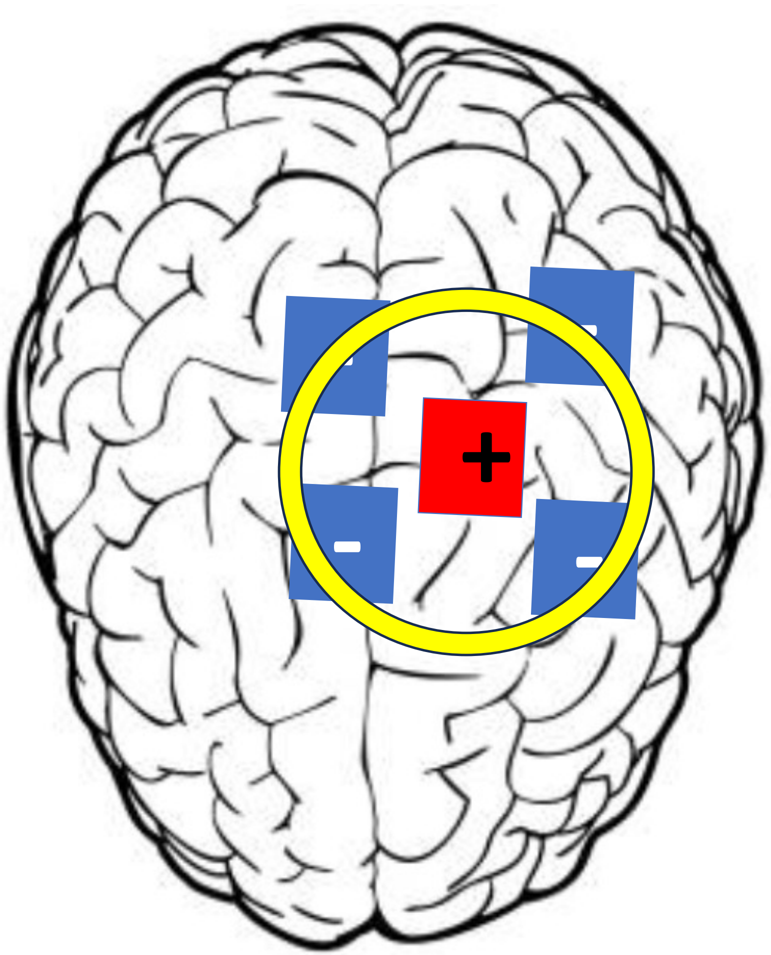


Making the ring small focuses brain targeting.

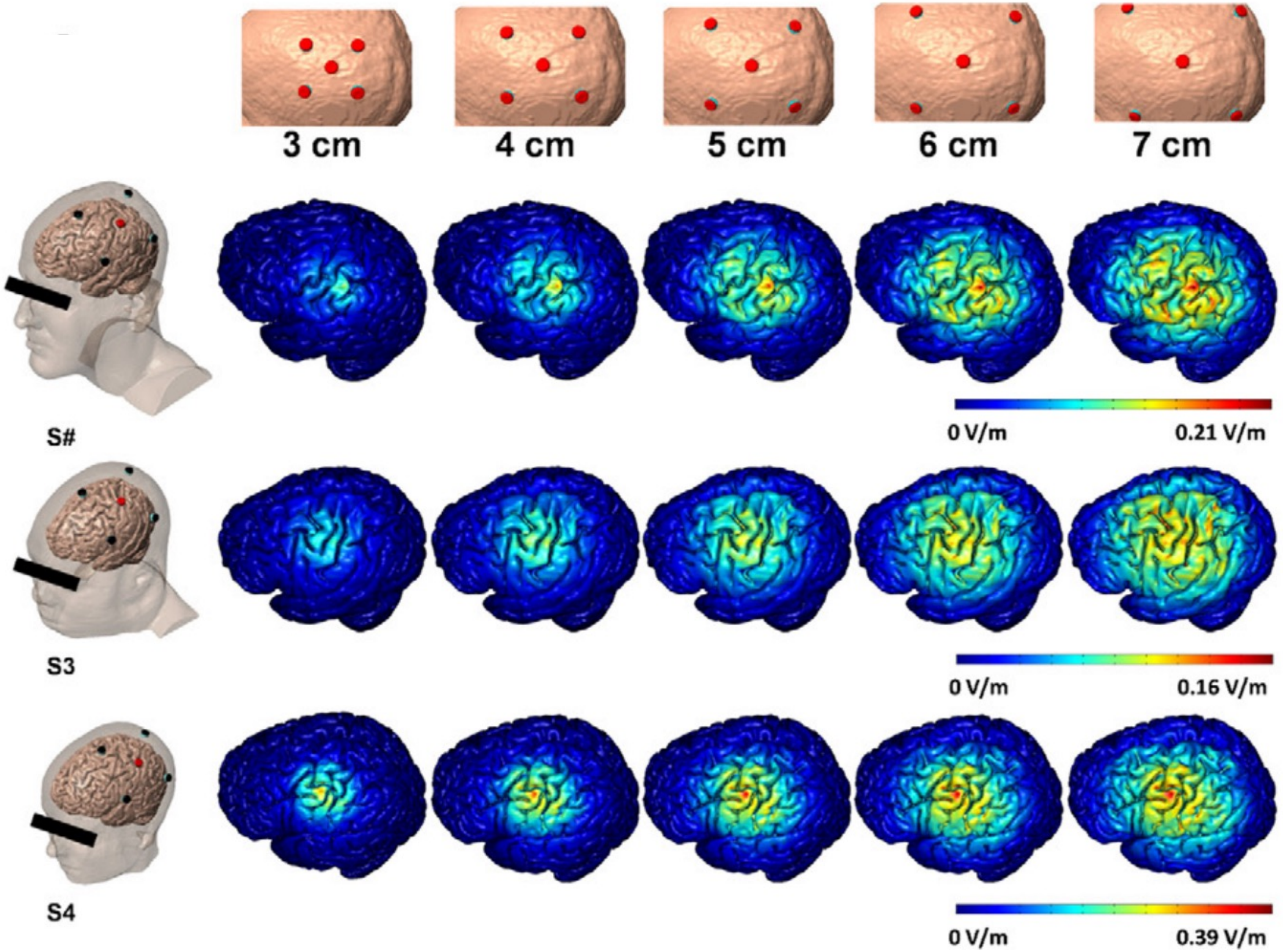


Making the ring small focuses brain targeting.

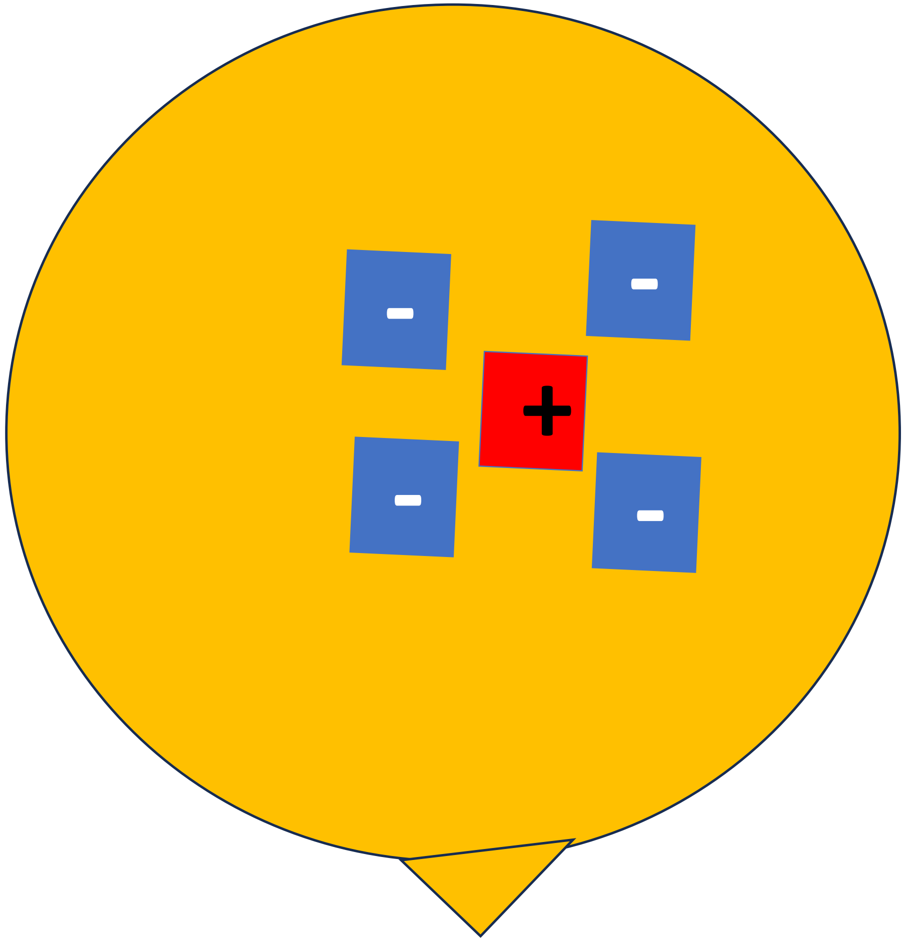
However, the intensity of current in the brain also decreases.

More focal.
Reduced intensity.

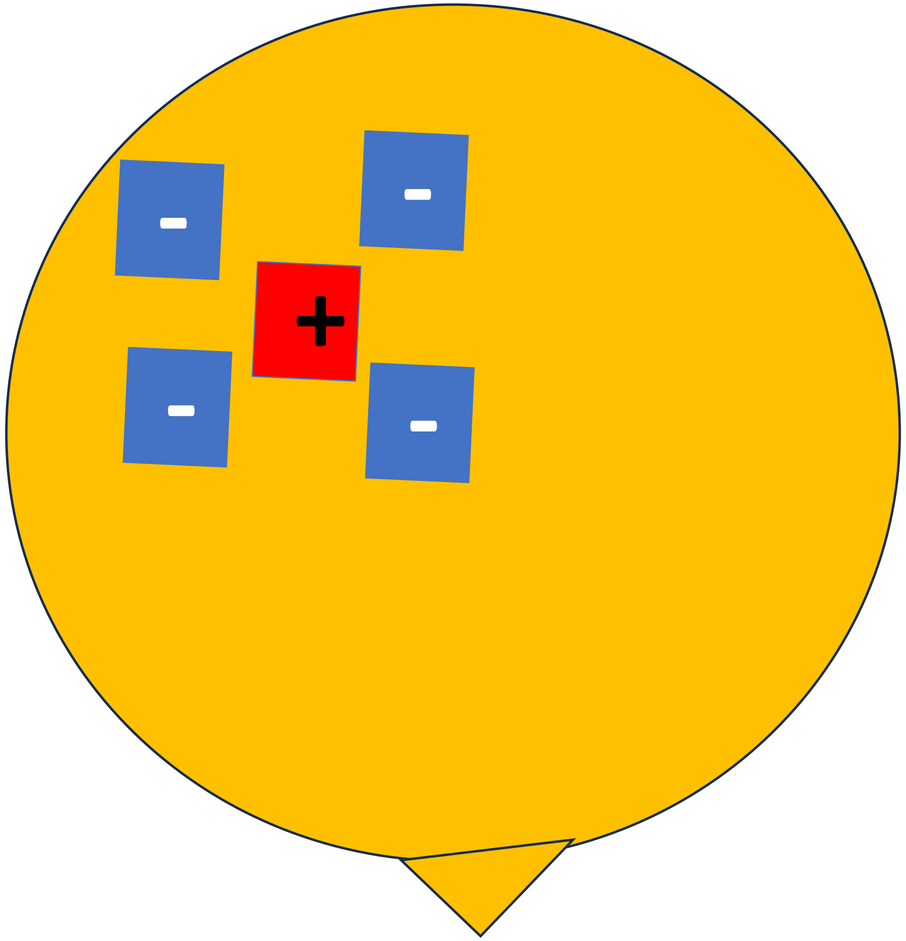
Reliably inside ring.



Alam et al. Spatial and polarity precision of concentric high-definition transcranial direct current stimulation (HD-tDCS). Physics in Medicine and Biology, 2016



Any cortical region can be targeted.



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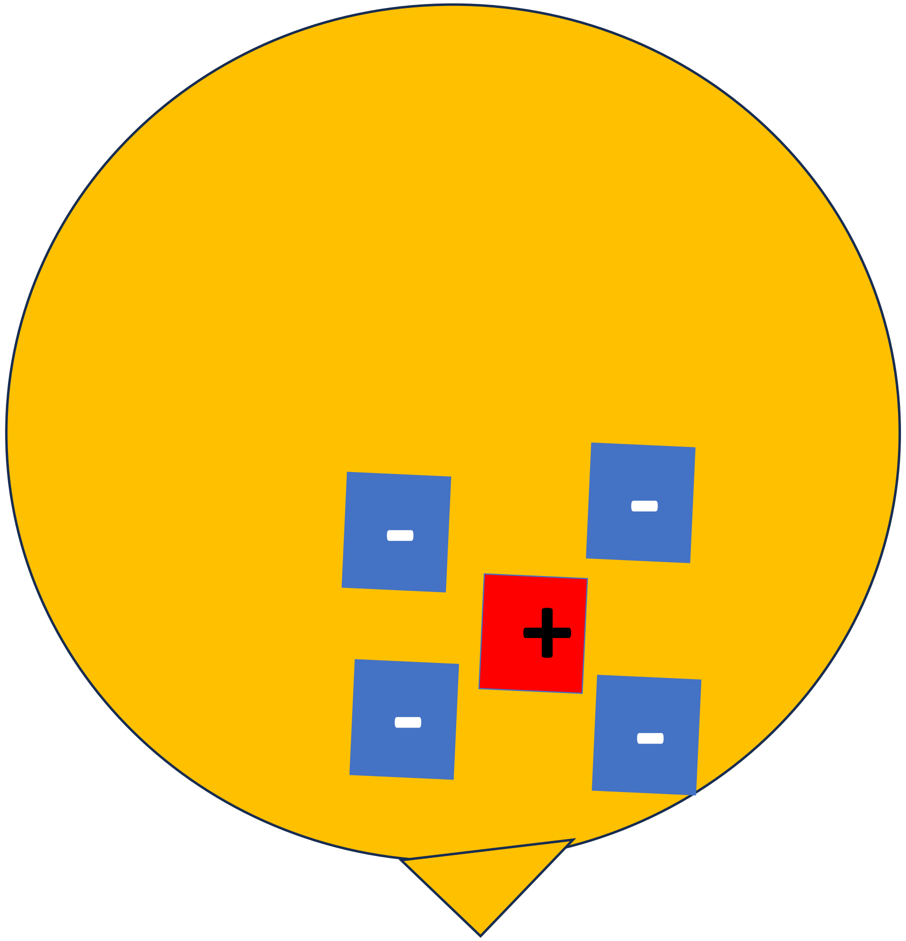

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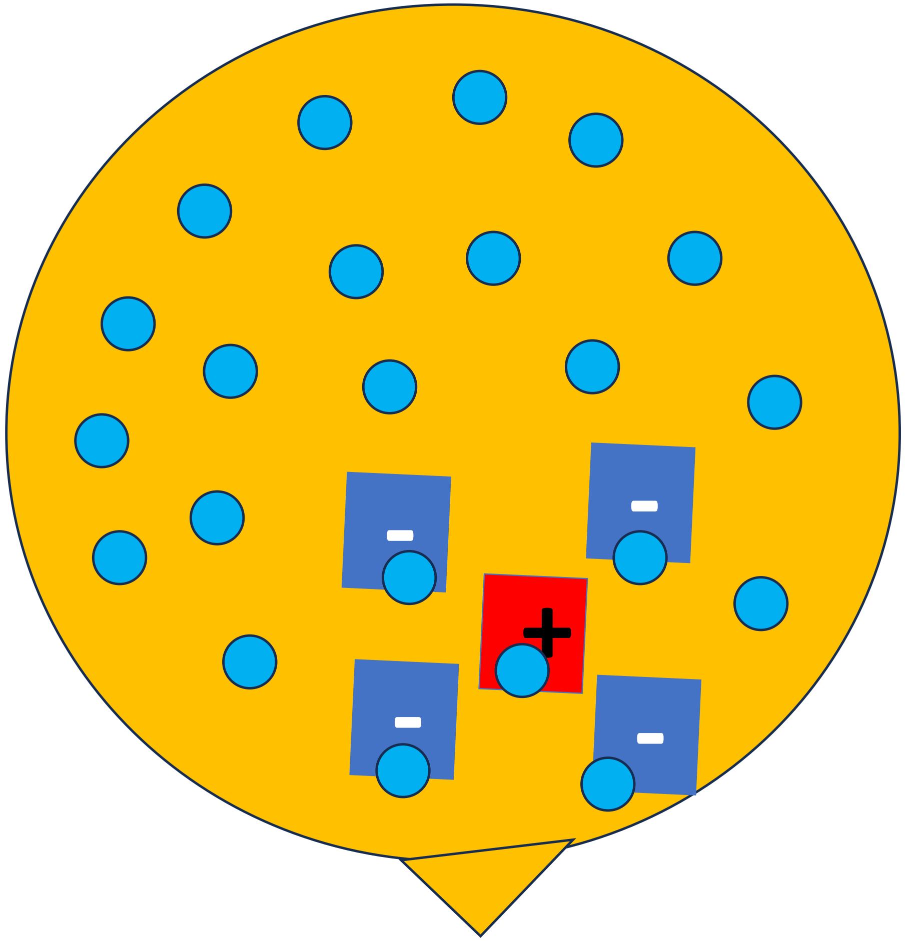
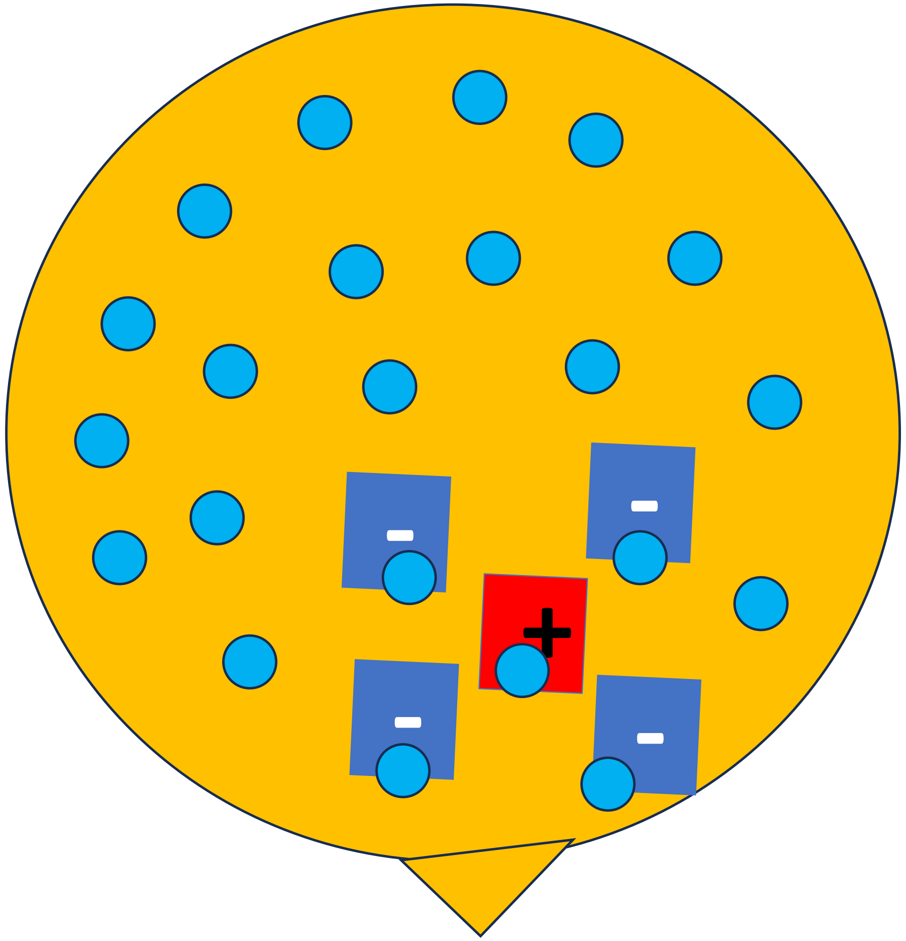


HD electrodes positioned according to EEG 10-10 system

Any cortical region can be targeted.



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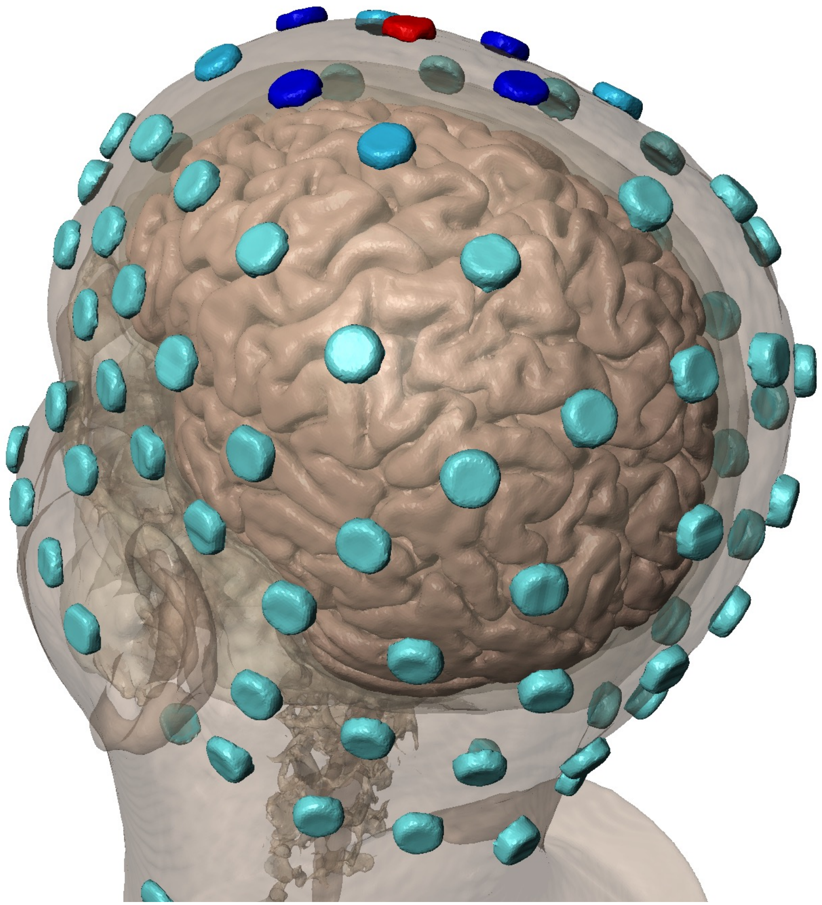
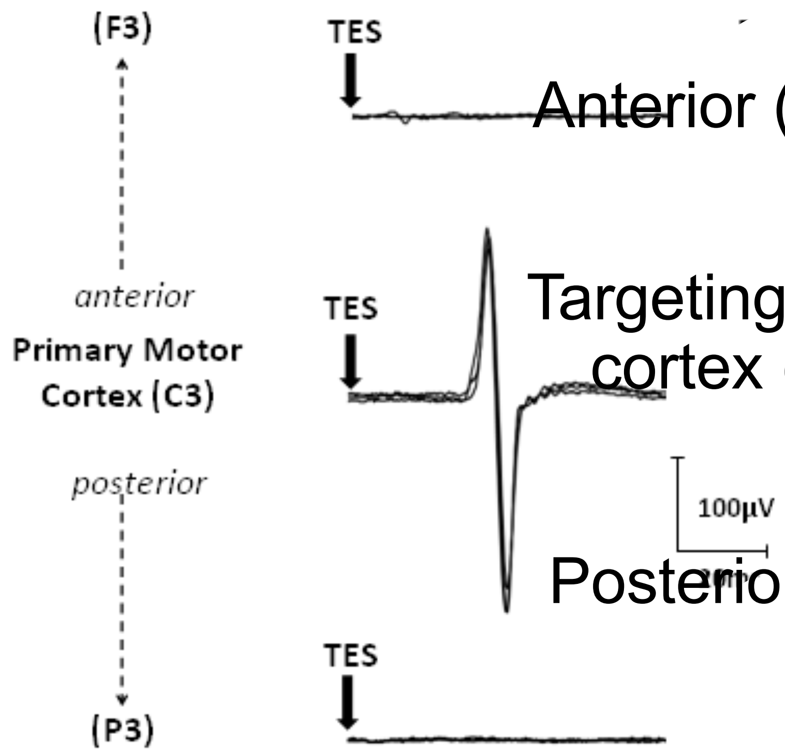


Just one problem

No one believed it (models)

4x1 HD electrodes

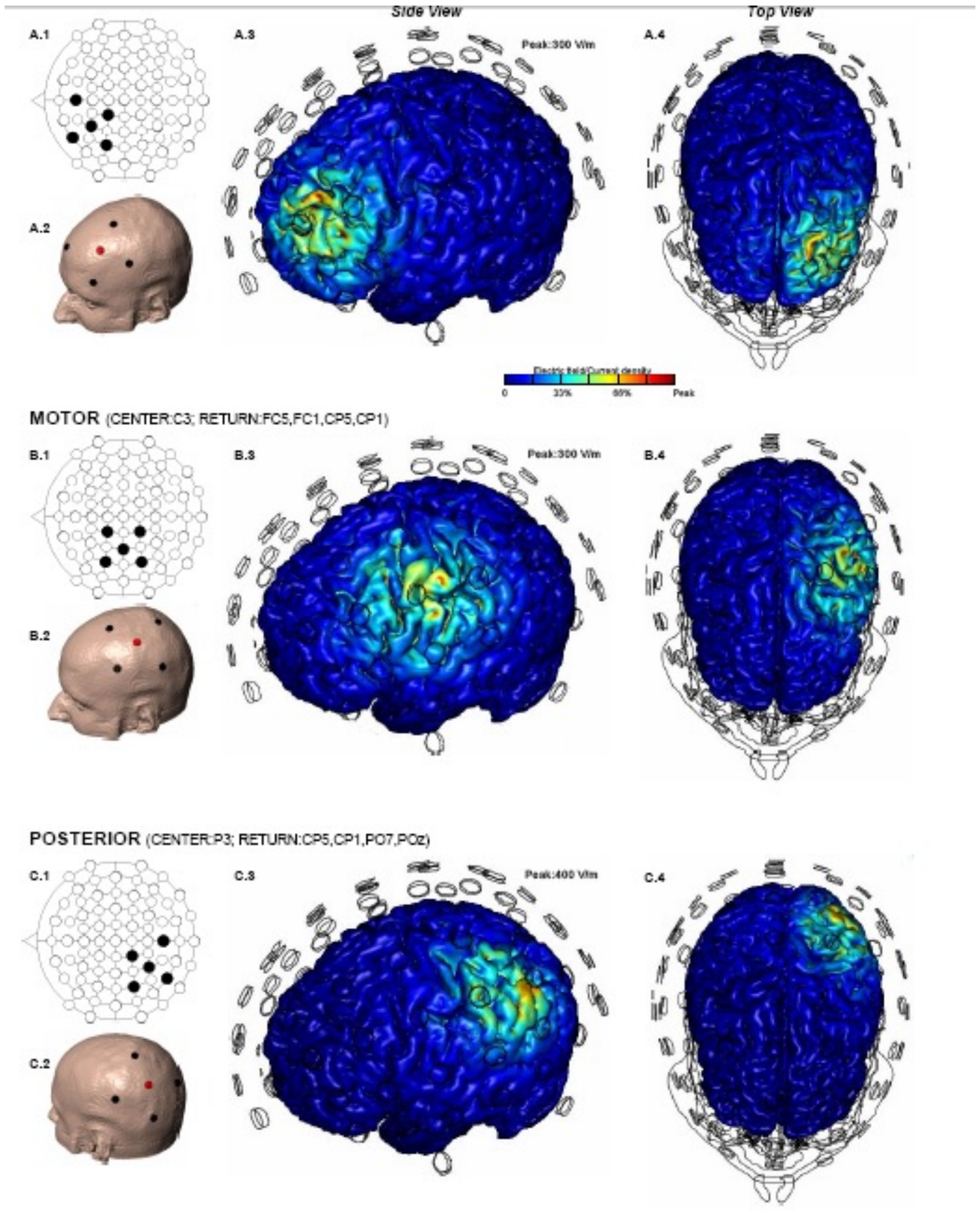
Using high-intensity (~1000 mA) pulse to trigger motor evoked potential (MEP)



Anterior (F3)

Targeting motor cortex (C3)

Posterior (P3)

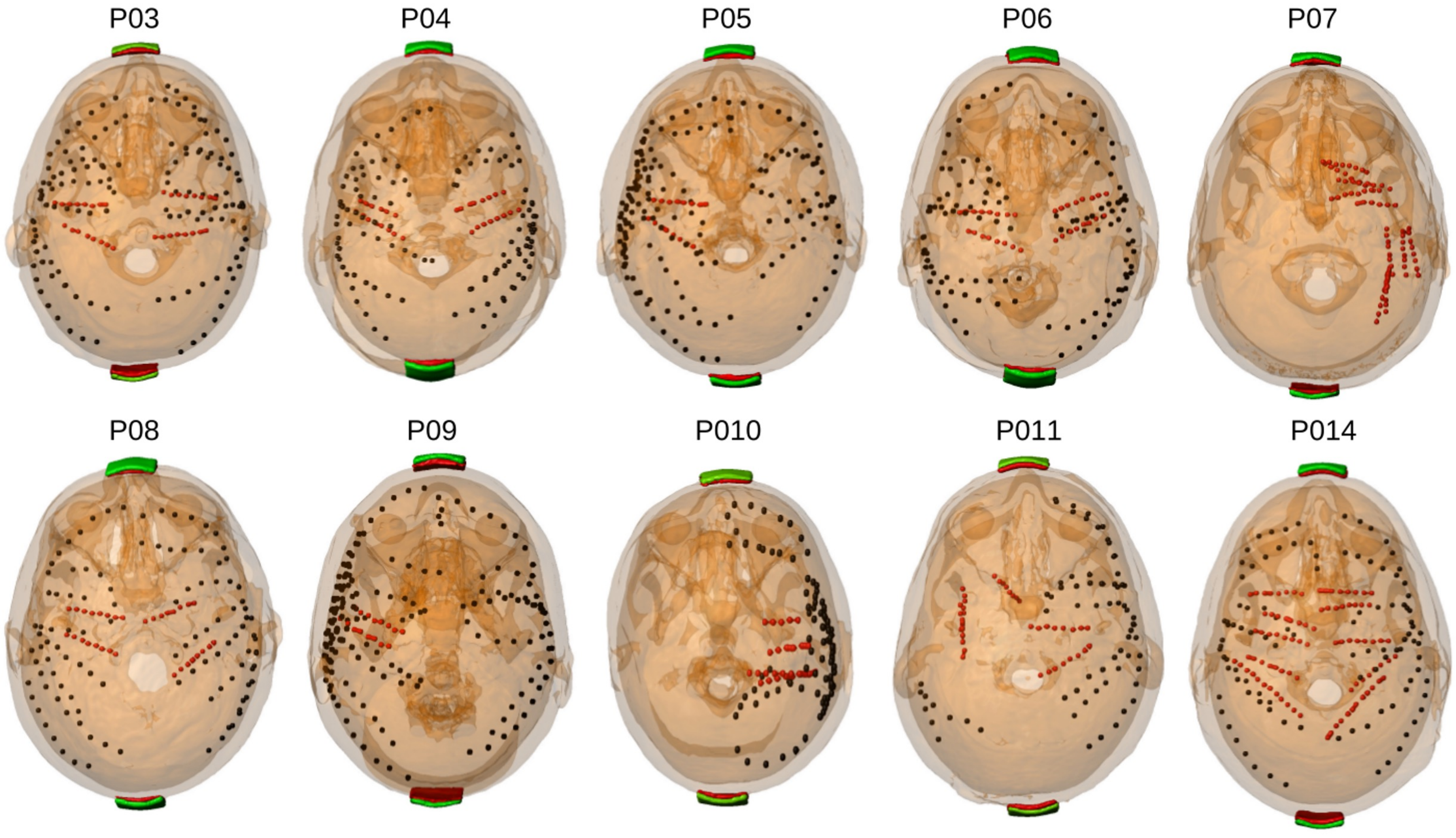


Edwards et al. Physiological and modeling evidence for focal transcranial electrical brain stimulation in humans. NeuroImage. 2013

Recordings inside the human brain confirm conventional tDCS is diffuse.

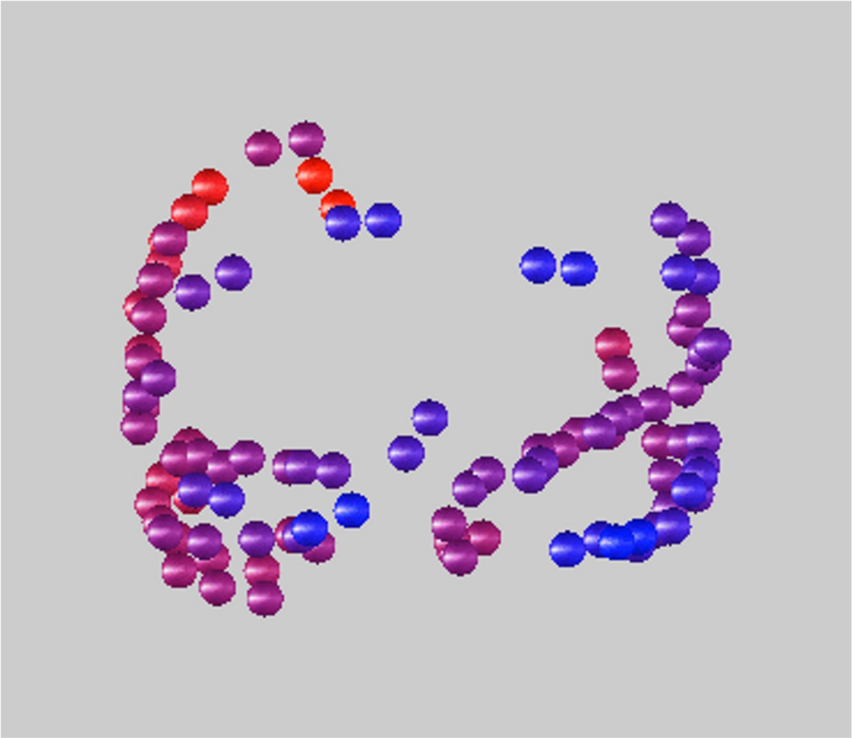
Intra-cranial voltages during transcranial electrical stimulation:

Experimental recordings with subject specific MRI-derived models.

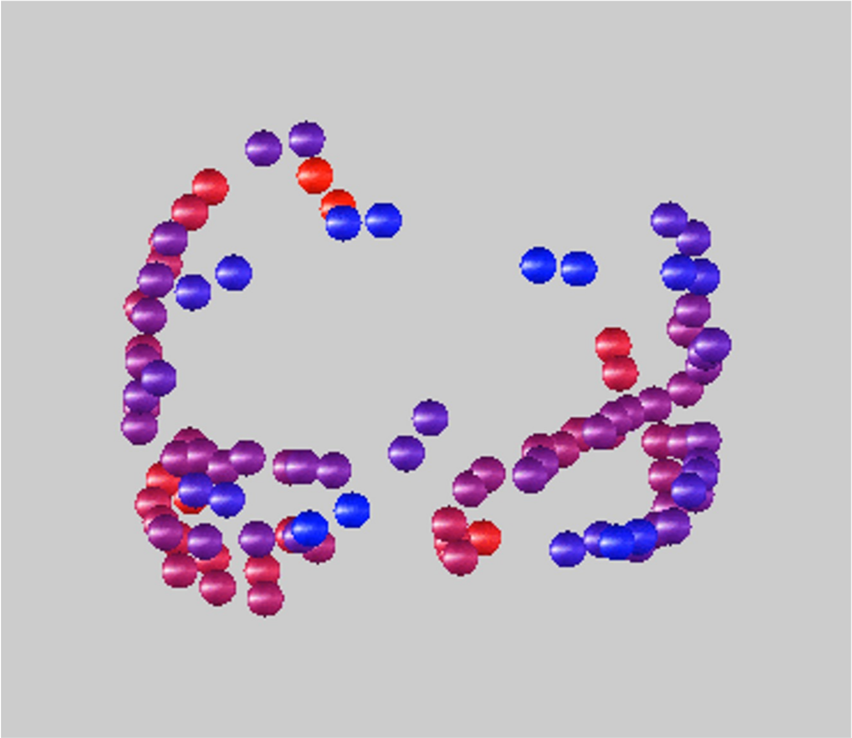


Huang et al. Measurements and models of electric fields in the human brain during tES. *Elife* 2017

Recordings inside the human brain confirm conventional tDCS is diffuse.

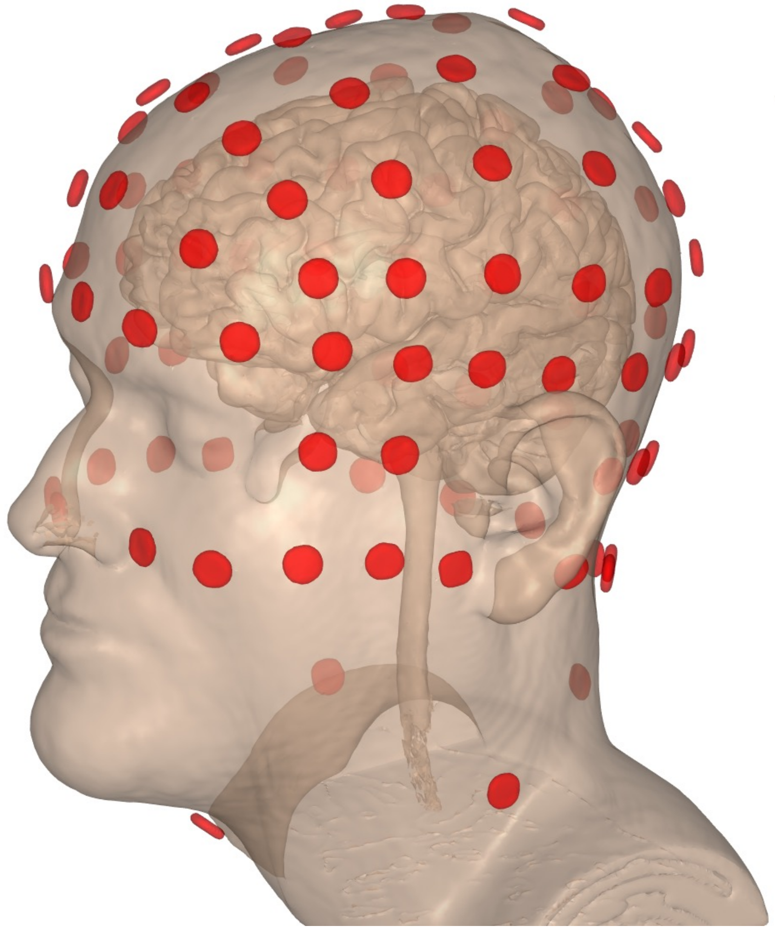


Recording (Volts)

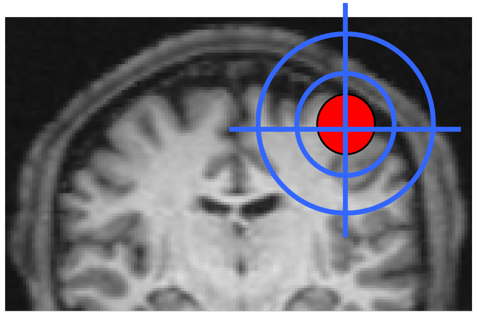


Model (Volts)

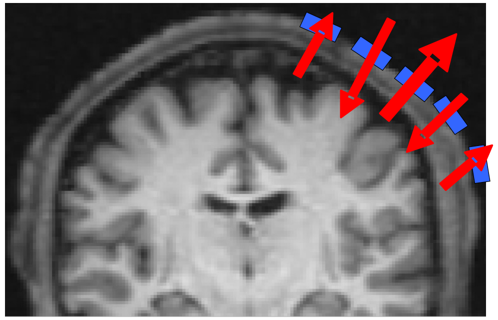
Huang et al. Measurements and models of electric fields in the human brain during tES. *Elife* 2017



Multi-electrode (MxN) HD-tDCS



Pick target and indicate number of electrodes (2, 4, …)



Software automatically determined HD configuration

- Trade-off between maximum intensity and maximum targeting

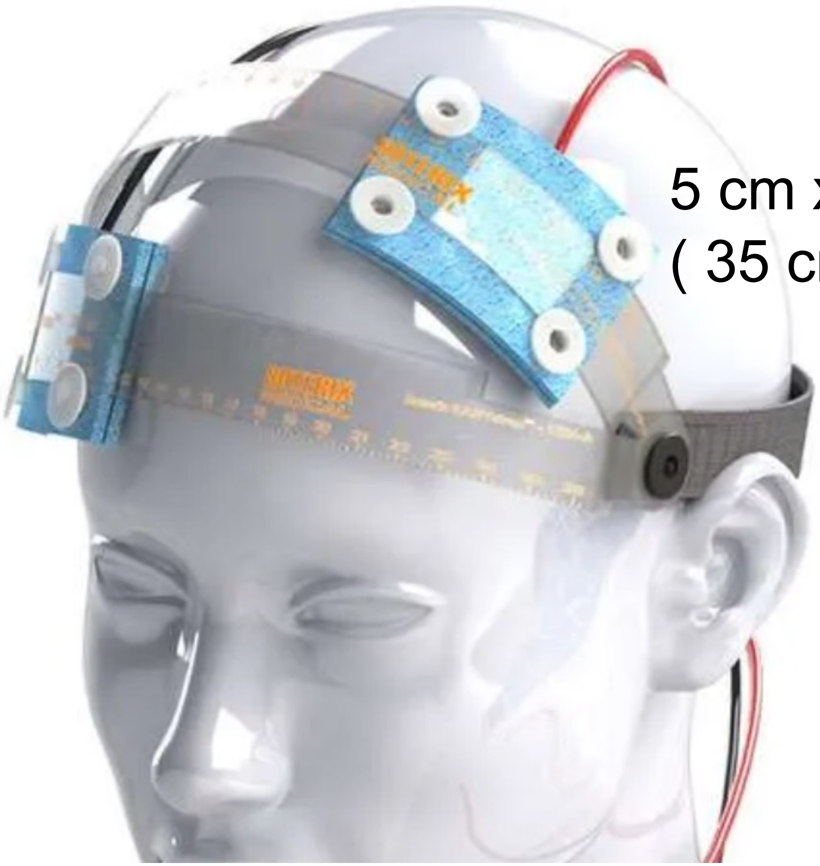
Dmochowski et al. Optimized multi-electrode stimulation increases focality and intensity at target. *Journal of Neural Engineering*. 2011

Just one problem, in 2009 High-Definition electrodes did not exist

And people said it was not possible.

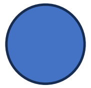
Current / electrode area = current density

Sponge electrode currents were limited ~2 mA, a higher current (current density) was painful



5 cm x 7 cm
(35 cm2)

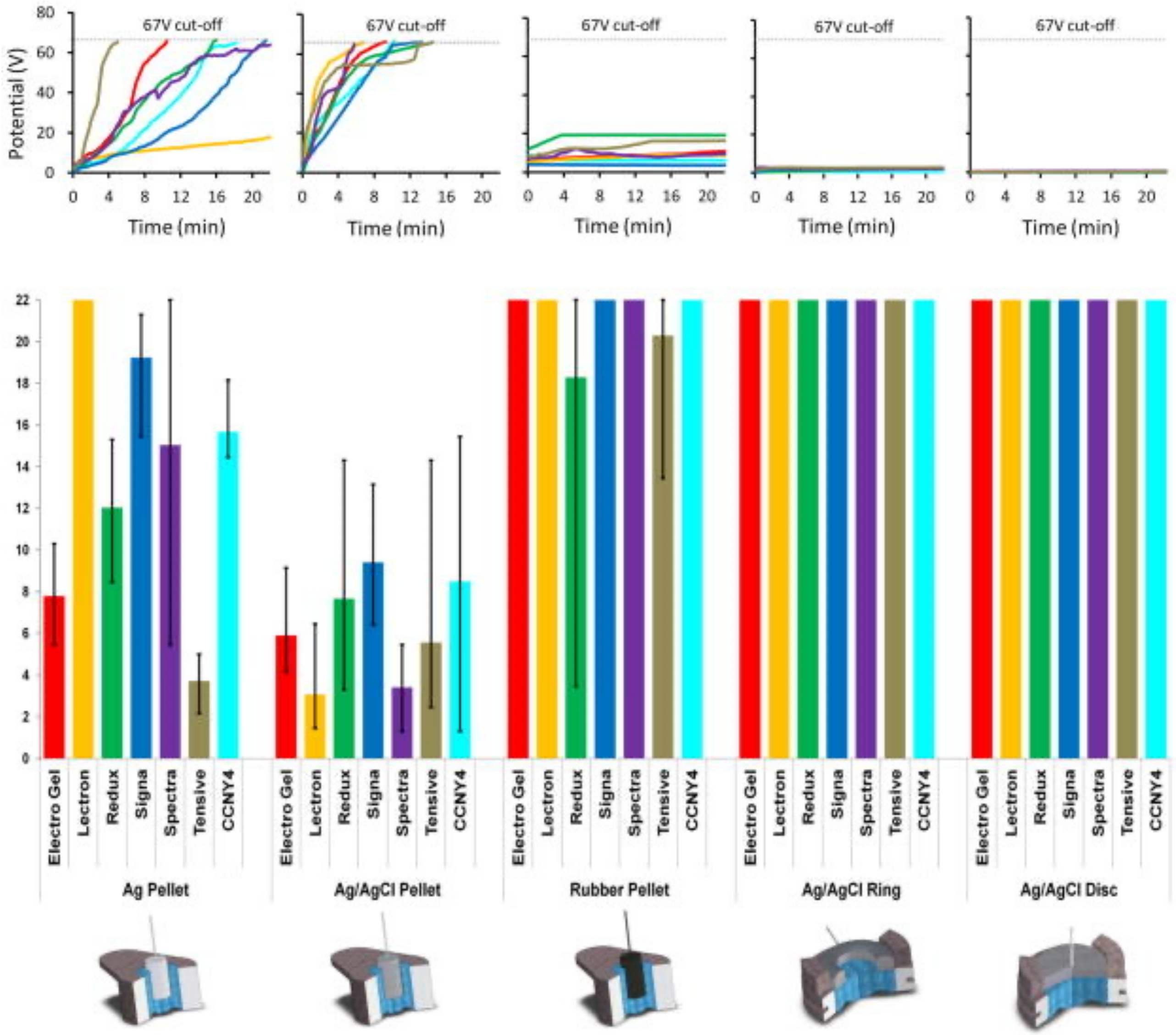
High-Definition electrodes <3.5 cm^2



Keeping the current same (needed for brain modulation) while making the electrodes smaller, would result in non-tolerated current density

Only 3 rules for a "good" non-invasive electrode

1) Doesn't hurt
2) Doesn't damage skin
3) Resistance not too high



BETTER. SMARTER.
Soterix medical

Minhas et al. 2010 Electrodes for high-definition transcutaneous DC stimulation for applications in drug delivery and electrotherapy, including tDCS, *Journal of Neuroscience Methods*

BETTER. SMARTER.
Soterix medical

Cap with High-Definition electrodes in it

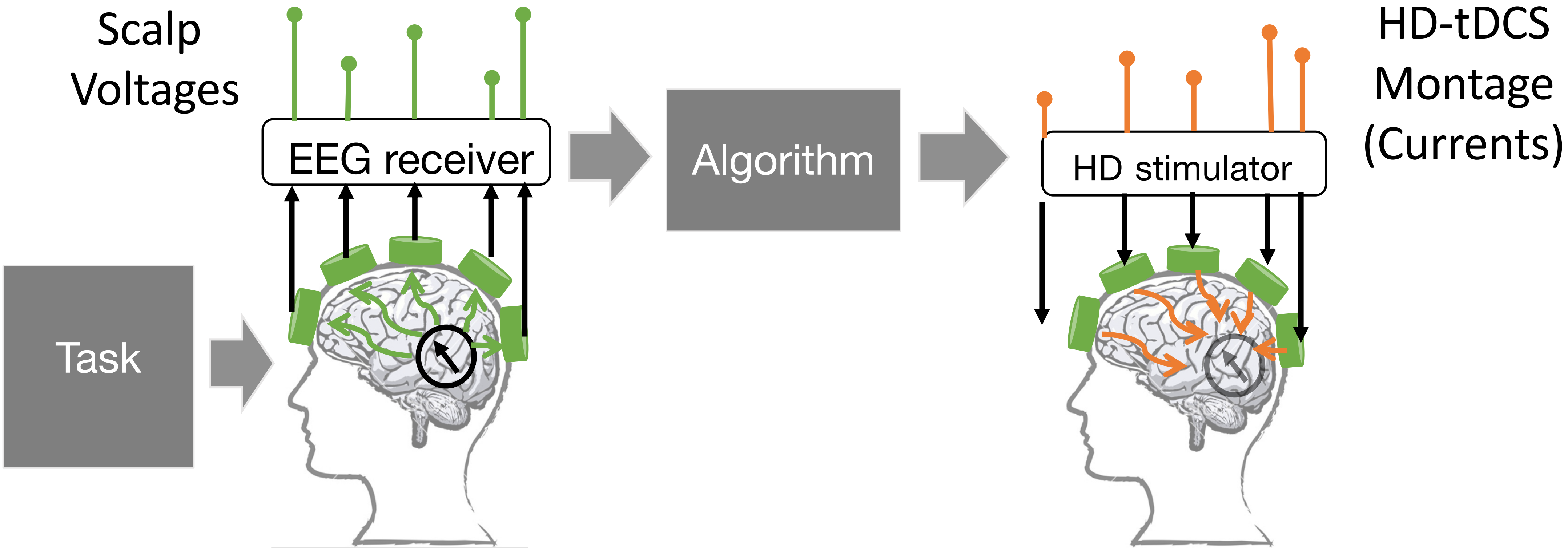
Software for simulating current flow

Fancy (multi-channel) function generator

HD-tDCS can be combined with EEG.

Dmochowski et al. Optimal use of EEG recordings to target active brain areas with transcranial electrical stimulation. *NeuroImage*. 2017

EEG recordings can automatically guide HD-tDCS targeting.



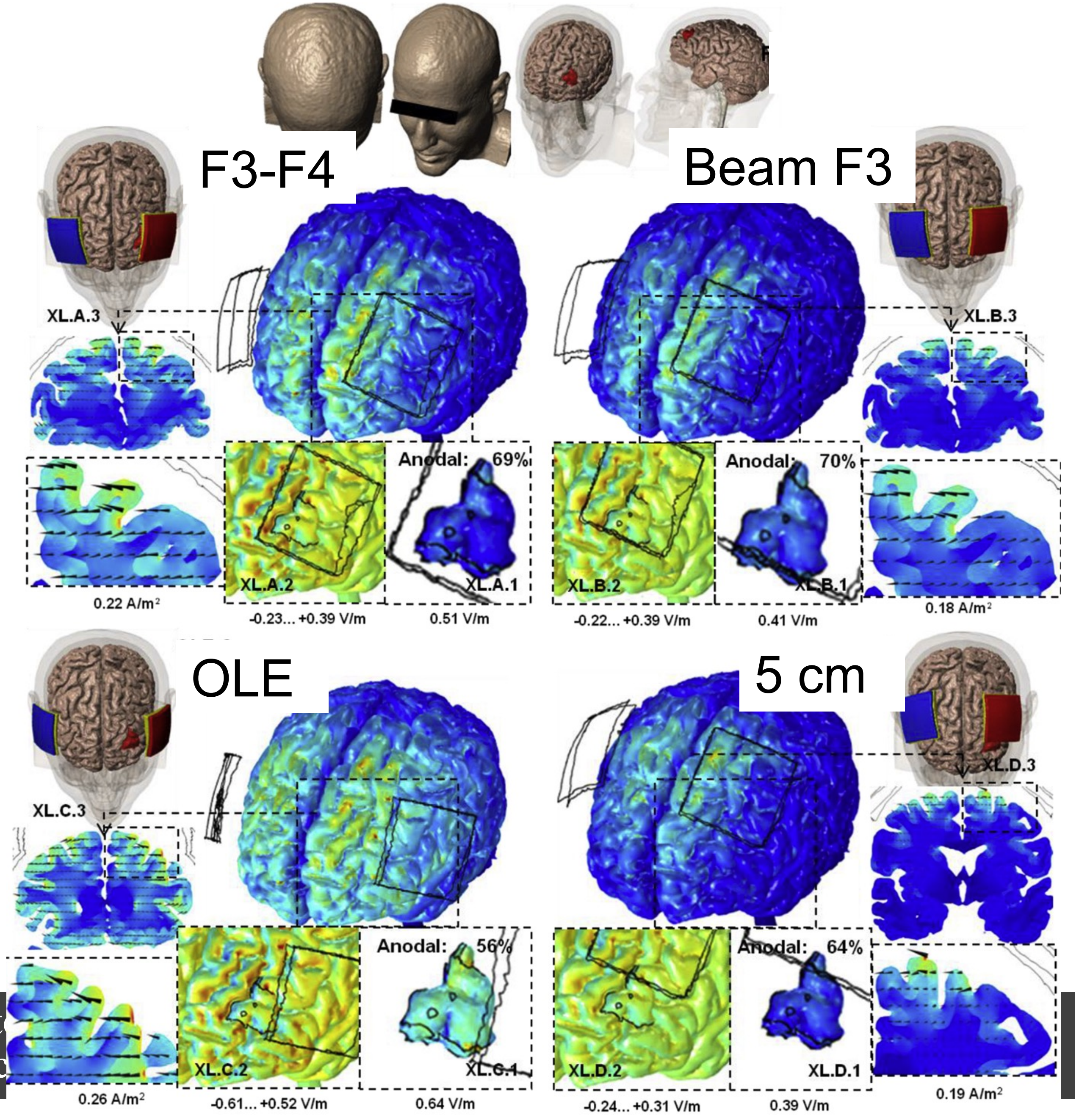
Dmochowski et al. Optimal use of EEG recordings to target active brain areas with transcranial electrical stimulation. *NeuroImage*. 2017

Conventional (pad) tDCS optimization: Intensity and direction at ”target” gyri.

Target: Anodal left DLPFC

No MRI / No Neuronavigation

Electrodes placed automatically using fixed position head-gear



Seibt et al. The pursuit of DLPFC: Non-neuronavigat
symmetric bicephalic transcranial direct c

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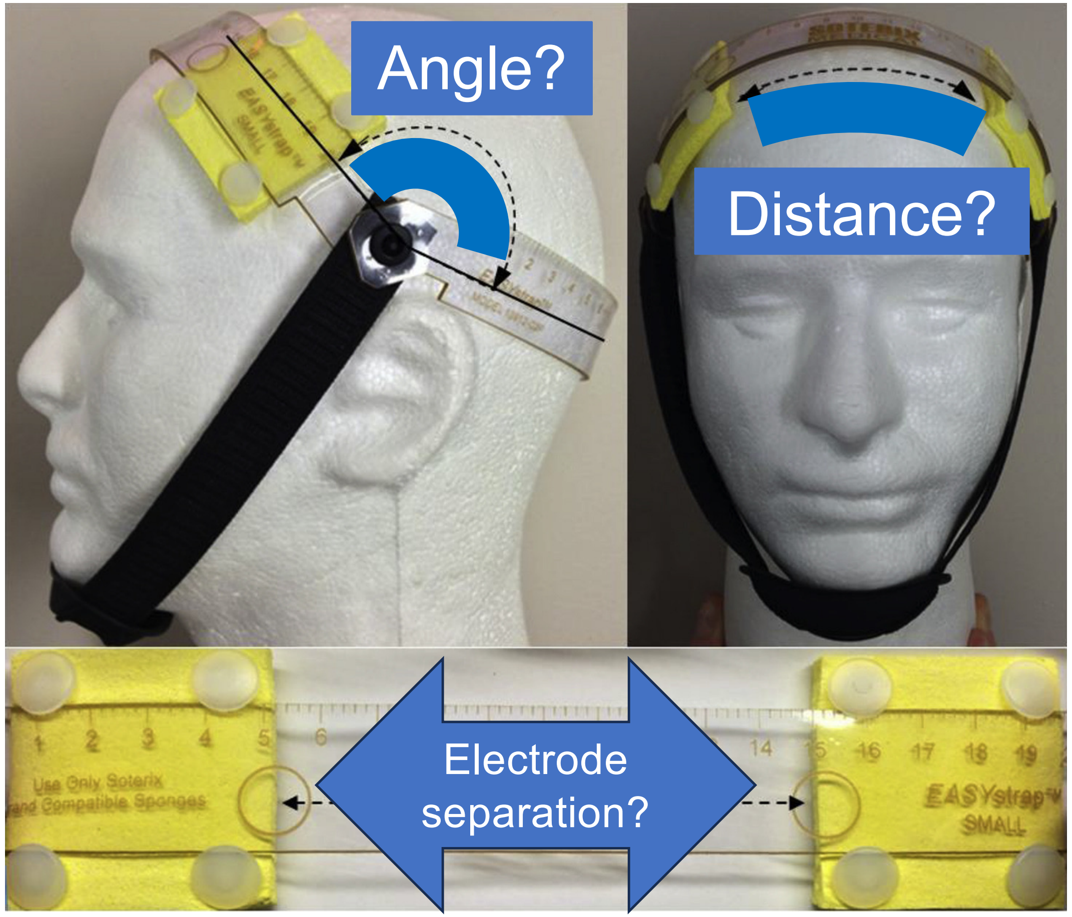
Omni-Lateral-Electrode (OLE) head-gear



Seibt et al. The pursuit of DLPFC: Non-neuronavigated methods to target the left dorsolateral pre-frontal cortex with symmetric bicephalic transcranial direct current stimulation (tDCS). *Brain Stimulation* 2015

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The NEW ENGLAND JOURNAL *of* MEDICINE

Trial of Electrical Direct-Current Therapy versus Escitalopram for Depression

A.R. Brunoni, A.H. Moffa, B. Sampaio-Junior, L. Borrione, M.L. Moreno, R.A. Fernandes, B.P. Veronezi, B.S. Nogueira, L.V.M. Aparicio, L.B. Razza, R. Chamorro, L.C. Tort, R. Fraguas, P.A. Lotufo, W.F. Gattaz, F. Fregni, and I.M. Benseñor, for the ELECT-TDCS Investigators*

JUNE 29, 2017

of placebo minus escitalopram), so noninferiority could not be claimed. Escitalopram and tDCS were both superior to placebo (difference vs. placebo, 5.5 points [95% CI, 3.1 to 7.8; P<0.001] and 3.2 points [95% CI, 0.7 to 5.5; P=0.01], respec-

INTERVENTIONS

Anode and cathode electrodes were placed over the left and right dorsolateral prefrontal cortexes, respectively, with the use of the Omni-Lateral-Electrode system.[12] In a total of 22 sessions that

Seibt et al. The pursuit of DLPFC: Non-neuronavigated methods to target the left dorsolateral pre-frontal cortex with symmetric bicephalic transcranial direct current stimulation (tDCS). *Brain Stimulation* 2015

How does putting a 9V battery on your head cure depression (etc.)?

What is **Supra-threshold Neuromodulation**

Stimulation waveforms built from pulses → Stimulation pulses driving some neurons to generate action potentials → Paced action potentials explain secondary (clinical) changes.

What is **Sub-threshold Neuromodulation**

Stimulation waveforms may or may not be pulsed based → Stimulation polarizes cells, changing how they function (process signals) → Secondary (clinical) changes

All neuromodulation (electrical stimulation) applied to the nervous system works by polarizing cells.

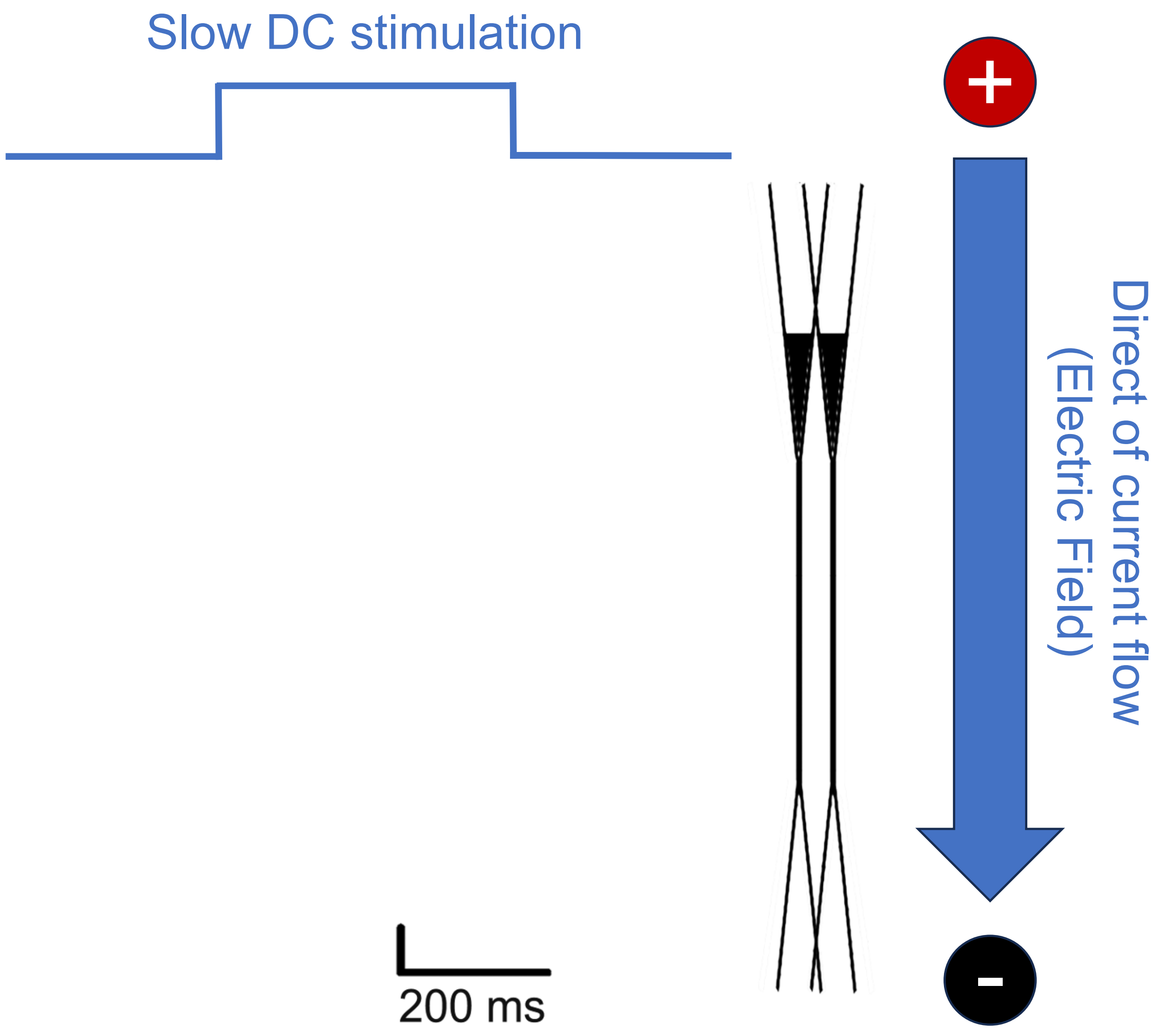
↓

Changing the membrane potential

The secret of sub-threshold neuromodulation:
The function of cells is changed even if the stimulation does not pace action potentials.

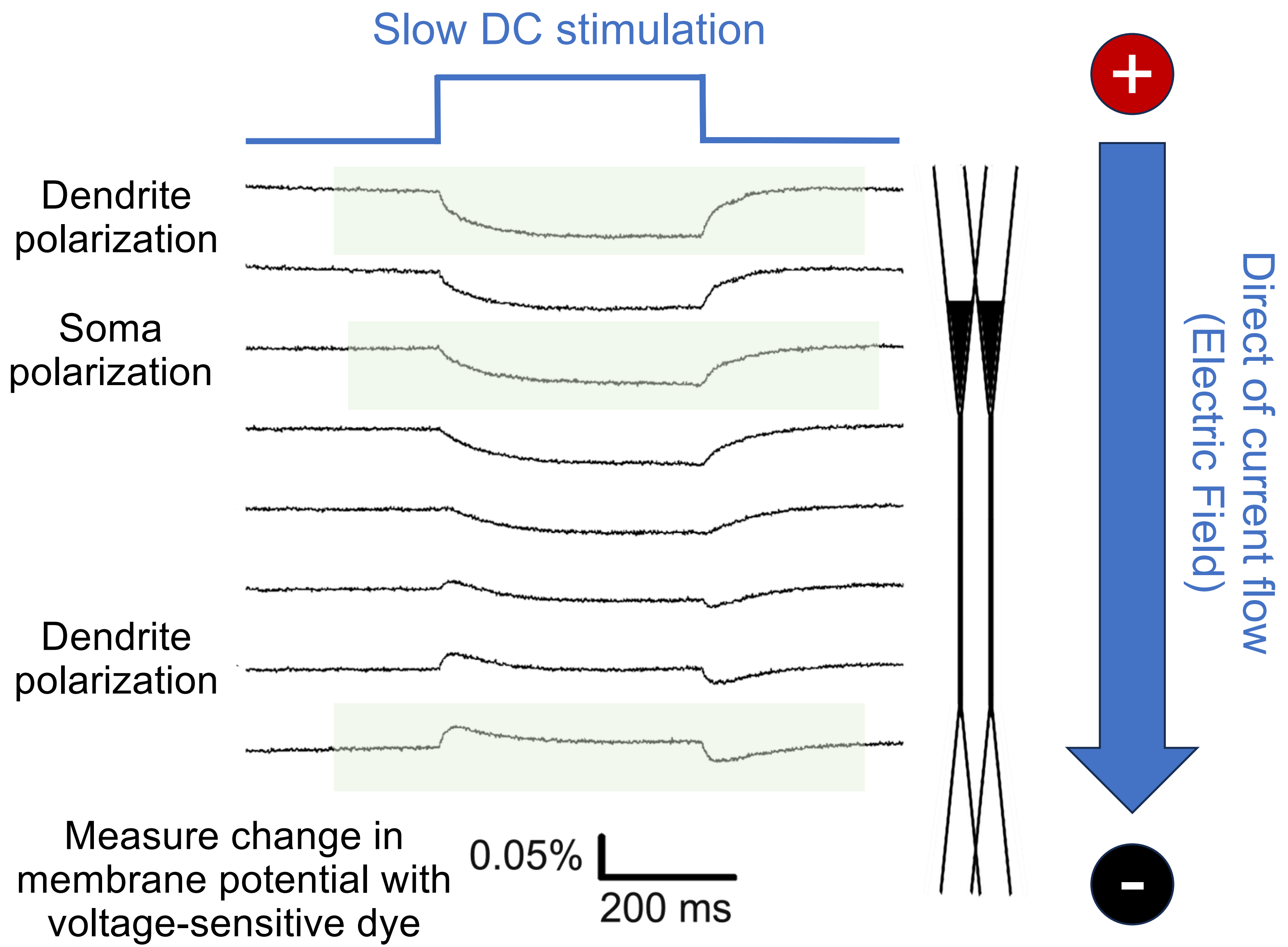
I will explain this in 7 points.

Thinking about long pulse (DC) low-intensity stimulation explains sub-threshold mechanism.



Bikson et al. Effects of uniform extracellular DC electric fields on excitability in rat hippocampal slice J Physiol 2004

1 Compartments of the cell all polarize but with different amount.



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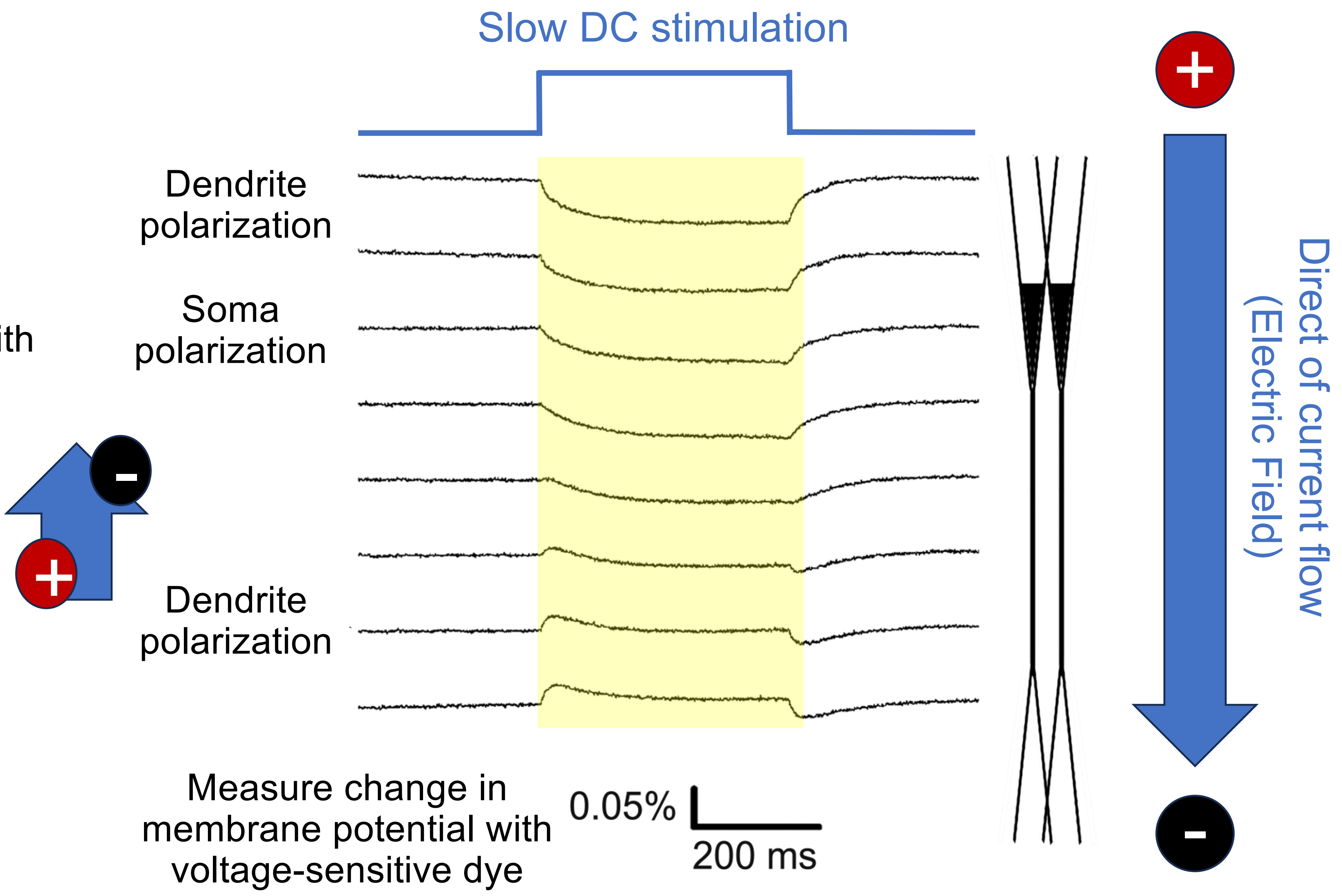
1. Compartments of the cell all polarize but with different amount.
2. The polarization "looks like" the stimulation. But with a charge up (time constant ~8 ms)
3. If you flip direction of current flow, you flip direction of polarization



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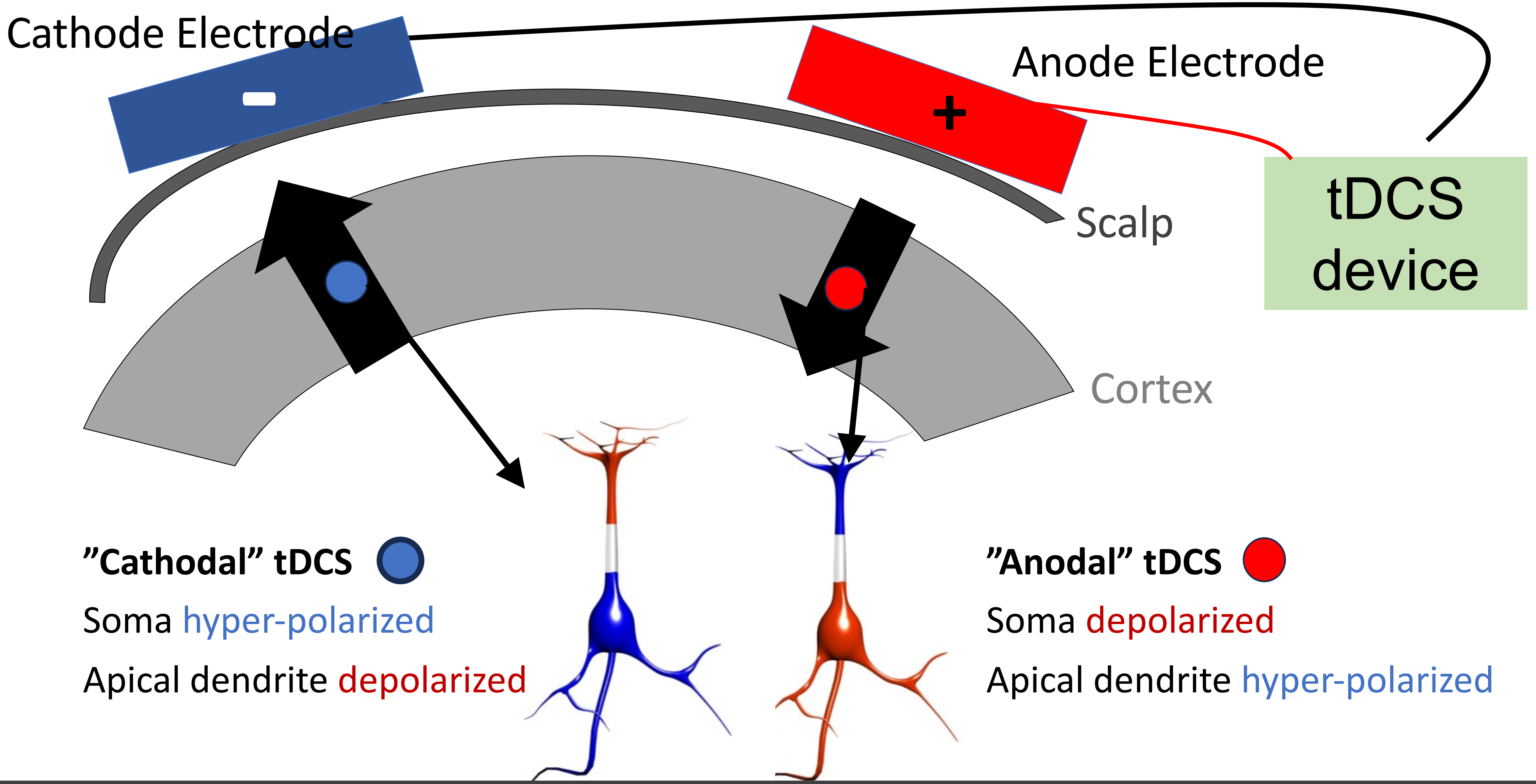

Radman et al. Role of cortical cell type and morphology in subthreshold and suprathreshold uniform electric field stimulation in vitro. . Brain Stimulation. 2009

1. Compartments of the cell all polarize but with different amount.
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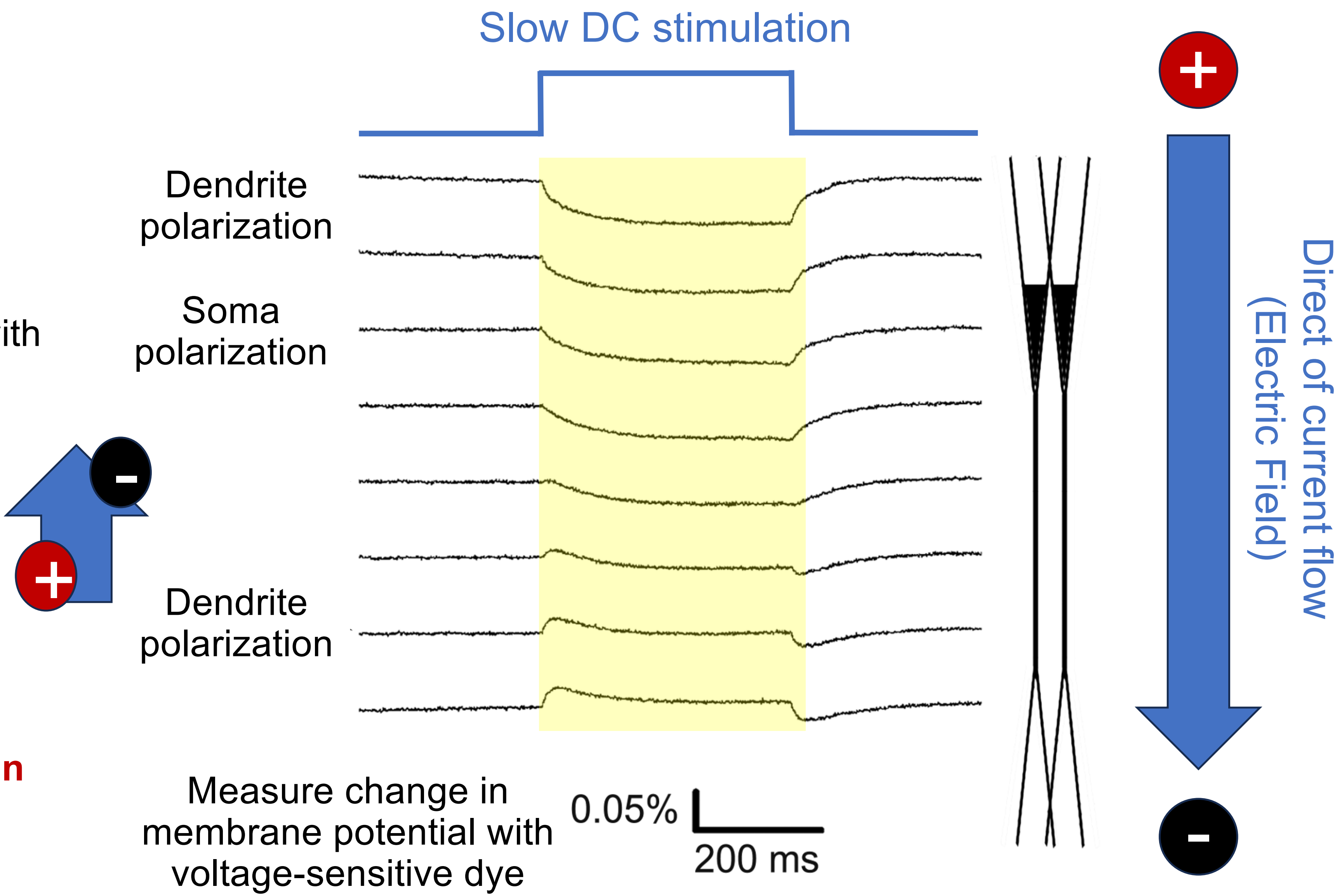
4. **Stimulation does not generate action potentials.**



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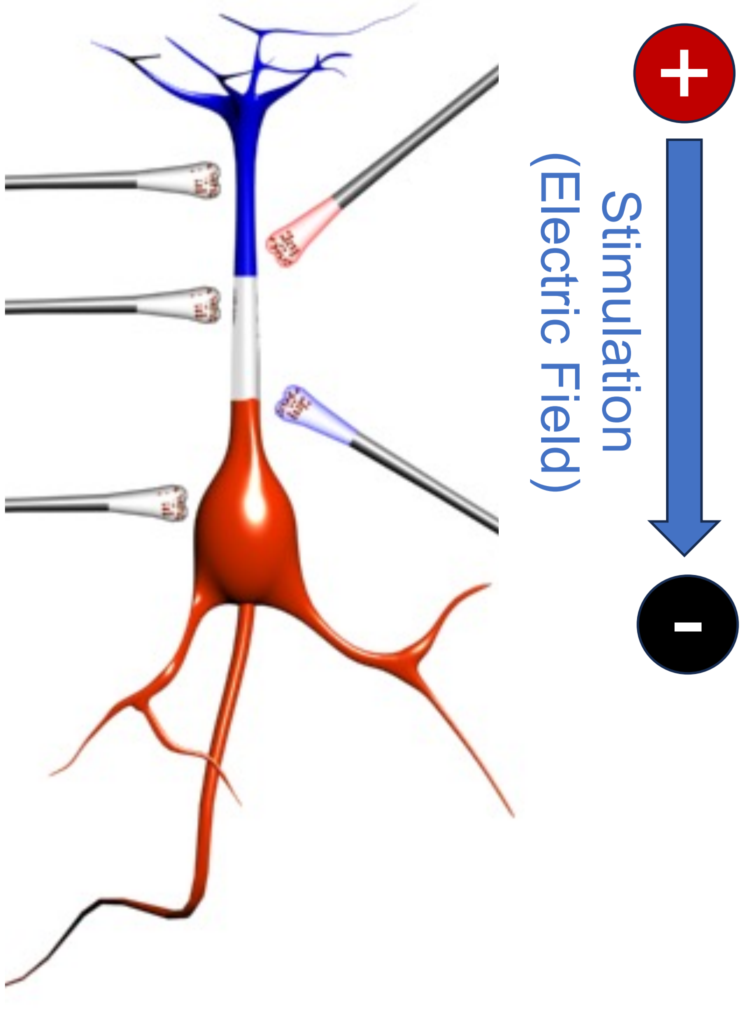
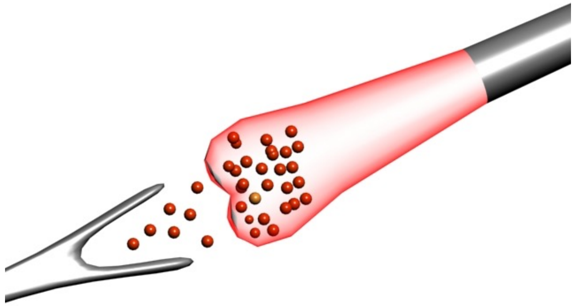
How do Electric Fields that are not large enough to trigger action potentials, but still produce neuronal polarization (of soma, dendrite, axon terminal) modulate brain function?



Not by generating action potentials but by changing the processing of ongoing activity including synaptic efficacy.

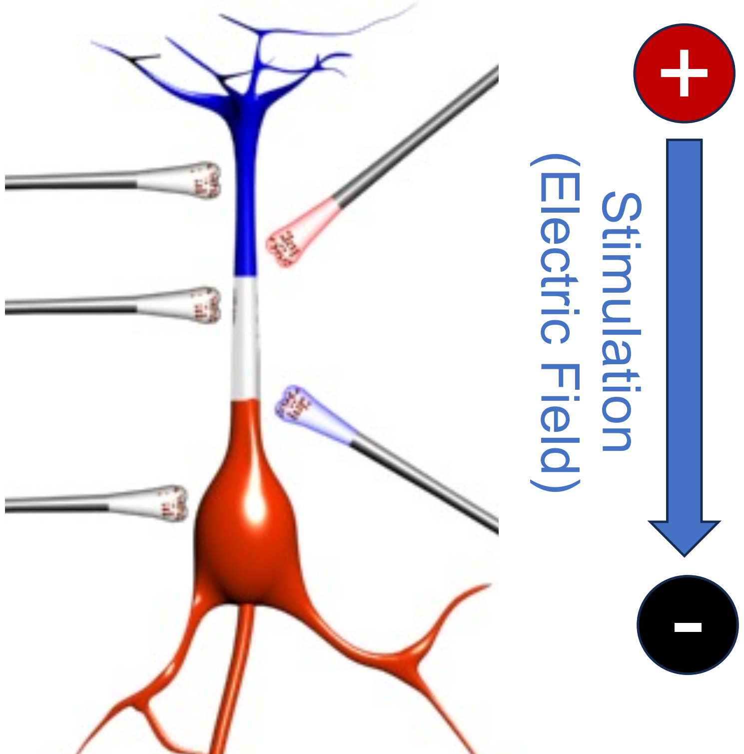
5

If a synapse is already active, how does the addition of polarization by an electric field change how the synapse works.



How neuron (compartment) polarization changes synaptic processing?

15 years of research in 60 seconds



Stimulation with long dc pulse

||||
Measure ongoing of specific synaptic pathway (field) excitatory post-synaptic potentials

||||
Measure modulation of ongoing activity

Lafon, Rahman et al. Direct Current Stimulation Alters Neuronal Input/Output Function. Brain Stim. 2017

Rahman et al. Cellular effects of acute direct current stimulation: somatic & synaptic terminal effects. J Physiol 2013

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How neuron (compartment) polarization changes synaptic processing?

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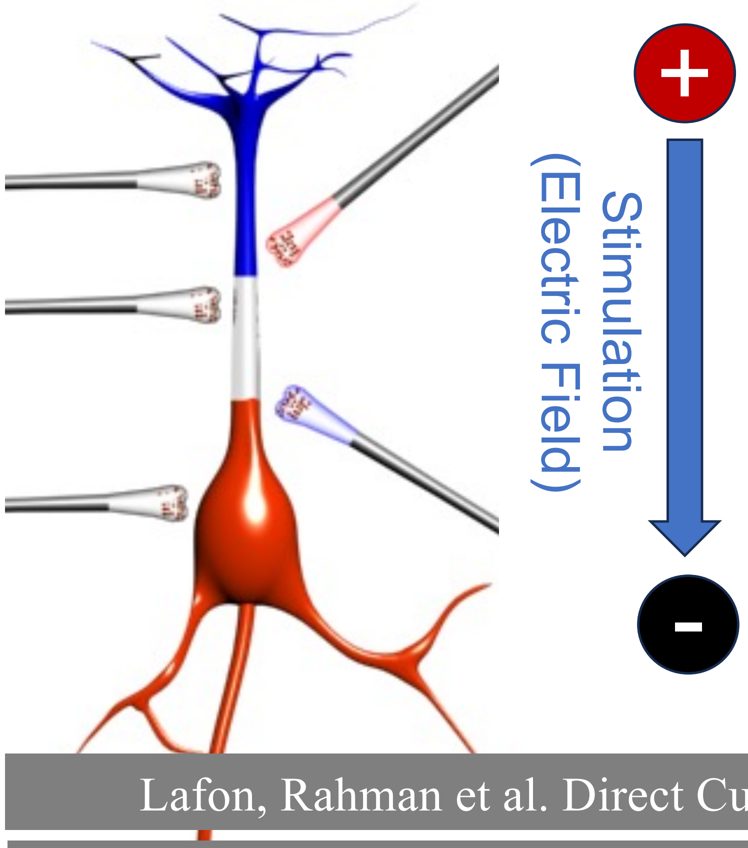
15 years of research in 60 seconds



The polarization of neuronal compartments involved in processing synaptic activity will of course change synaptic efficacy.

- Axon terminal (synapse) hyperpolarization favors increased synaptic efficacy.
- Dendrite hyperpolarization favors increased synaptic current.
- Soma depolarization favors lowering action potential threshold.

~1% change in synaptic efficacy per V/m electric field

Lafon, Rahman et al. Direct Current Stimulation Alters Neuronal Input/Output Function. Brain Stim. 2017

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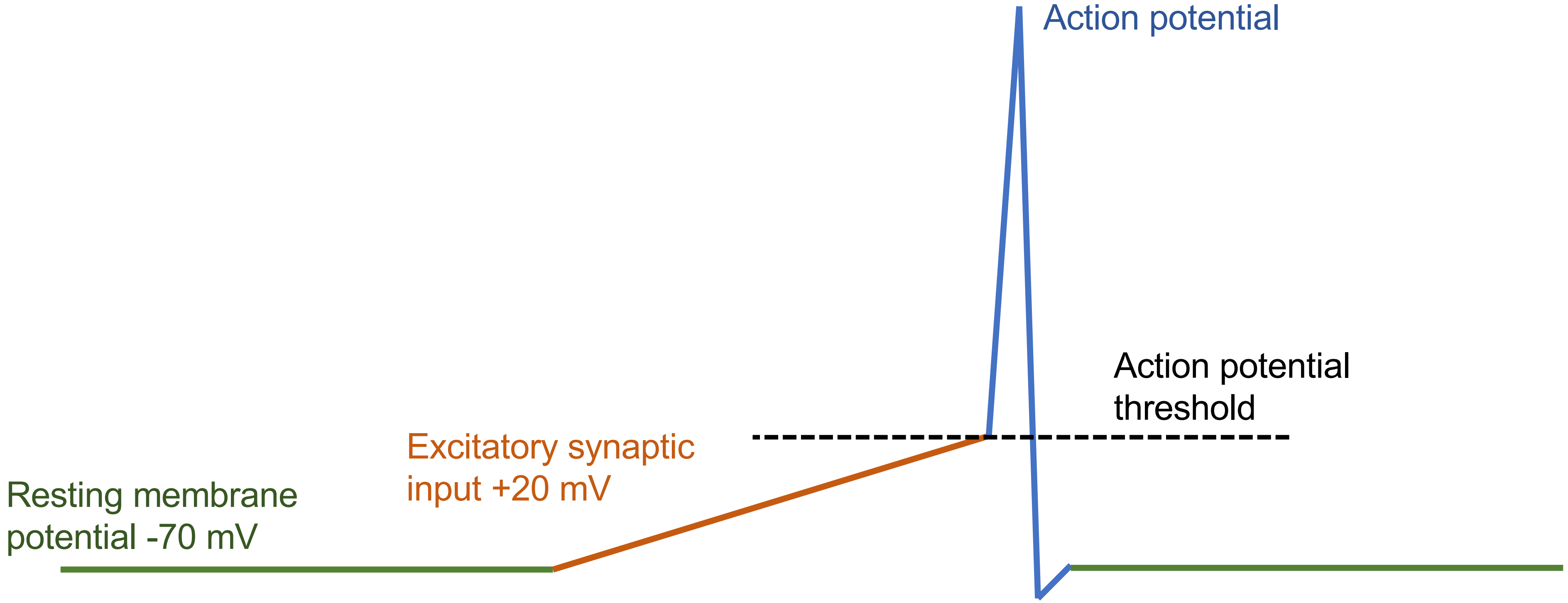
Brain function depends on action potentials. Sub-threshold stimulation must ultimately modulate action potentials to change brain function.
This is not by pulse-based pacing but rather changing how ongoing activity might lead to action potentials.



Radman et al. Spike timing amplifies the effect of electric fields on neurons. J Neurosci 2007

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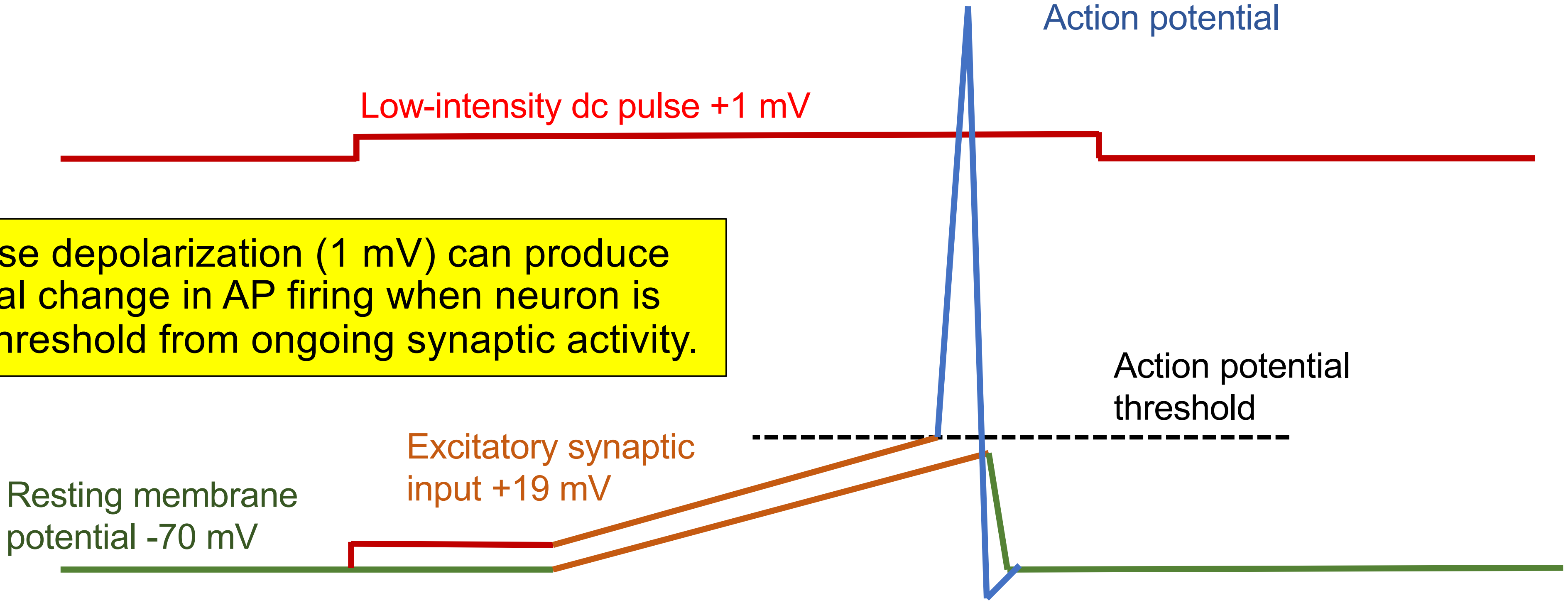

Small pulse depolarization (1 mV) can produce categorical change in AP firing when neuron is close to threshold from ongoing synaptic activity.

Radman et al. Spike timing amplifies the effect of electric fields on neurons. J Neurosci 2007

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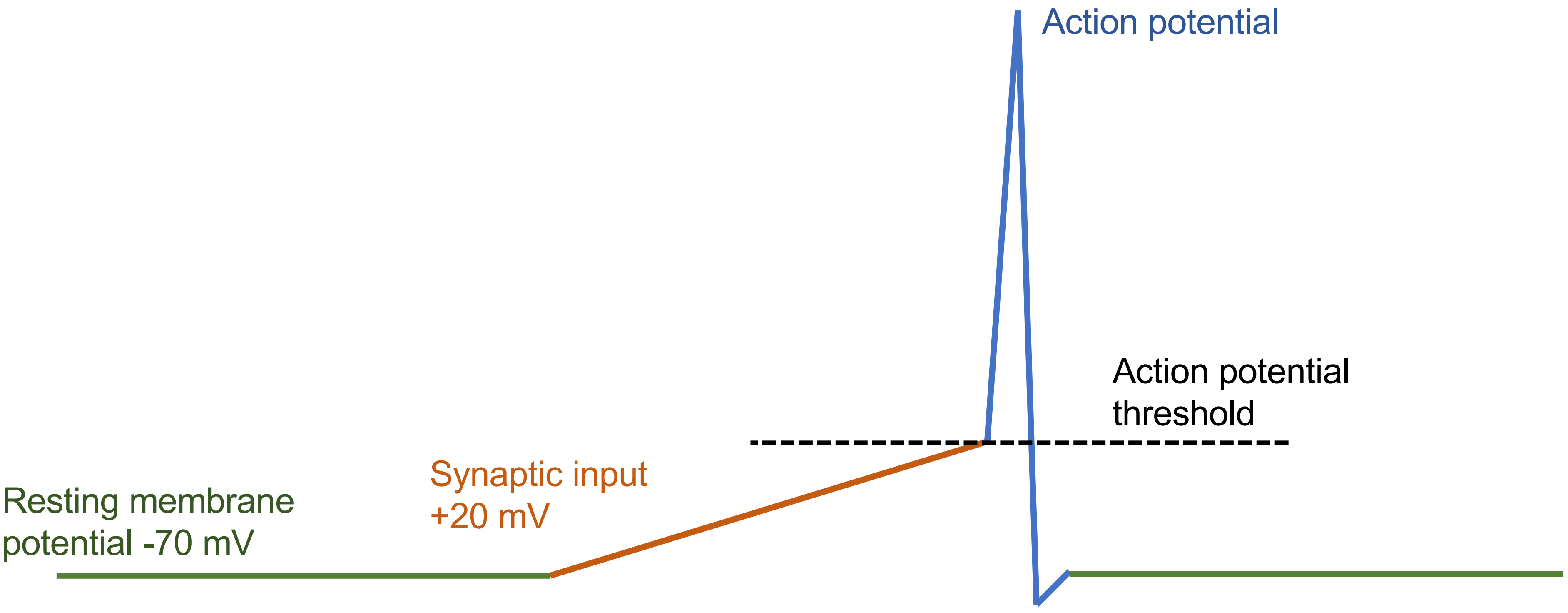

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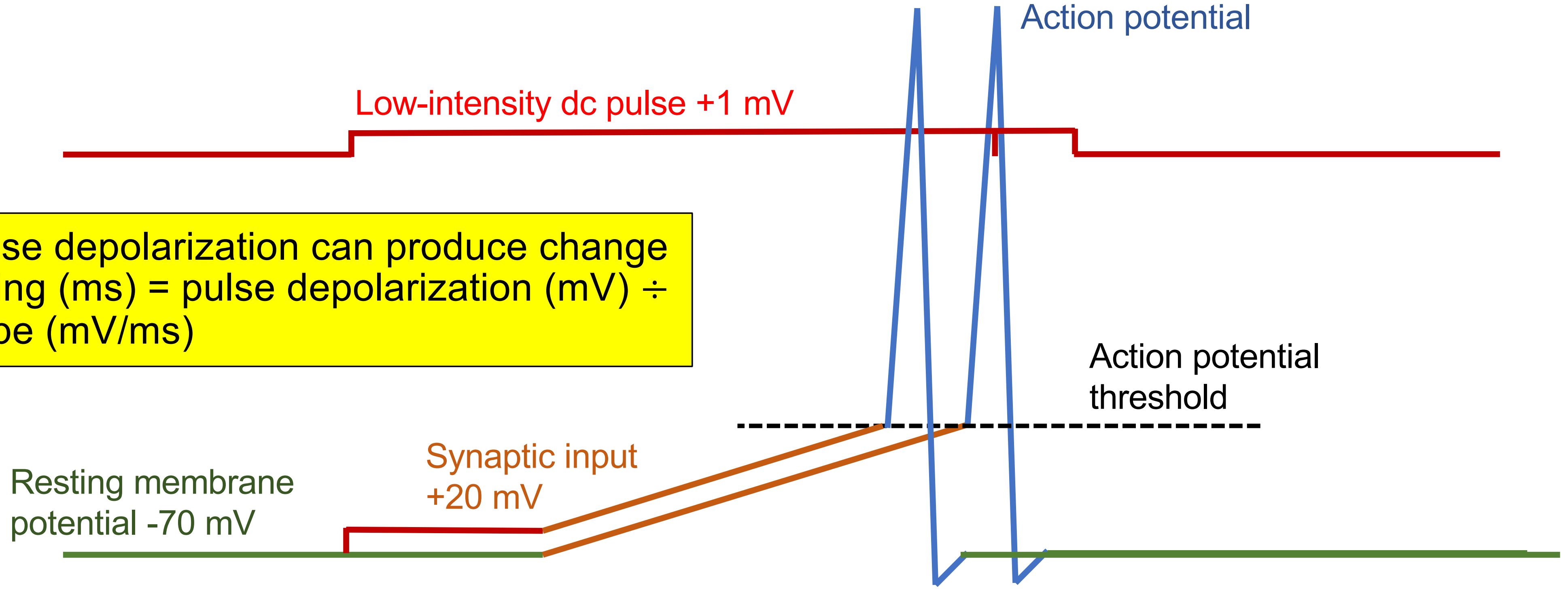
Small pulse depolarization can produce change in AP timing (ms) = pulse depolarization (mV) ÷ ramp slope (mV/ms)



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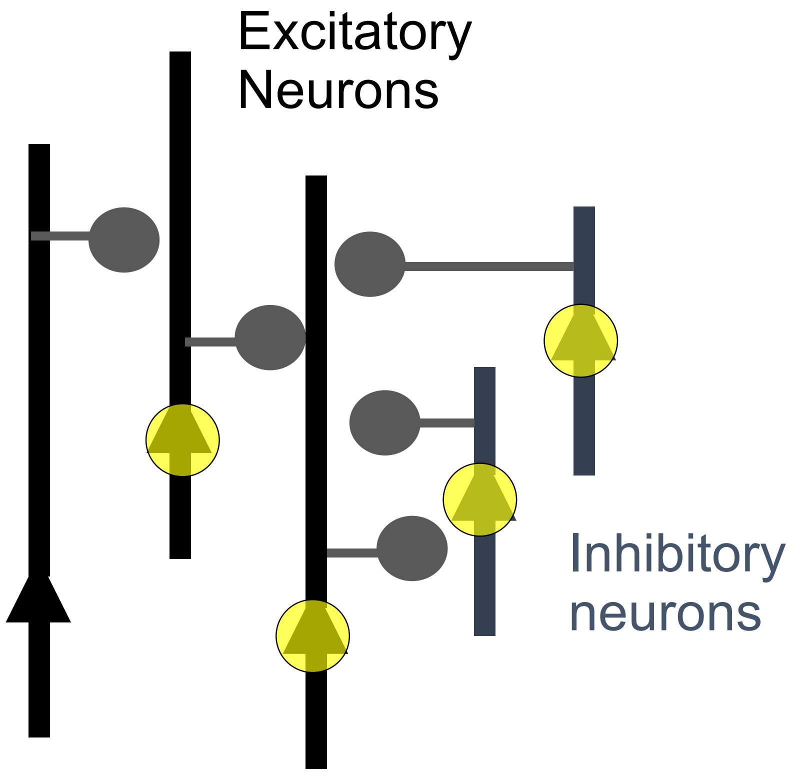
7

Oscillations are network brain states with many neurons closed/crossing action potential threshold, making individual neurons in the network sensitive to sub-threshold stimulation. The cohesion of the network itself provides further sensitization.



Reato, Rahman, Bikson & Parra. Low-intensity electrical stimulation affects network dynamics by modulating population rate and spike timing. J Neurosci 2010

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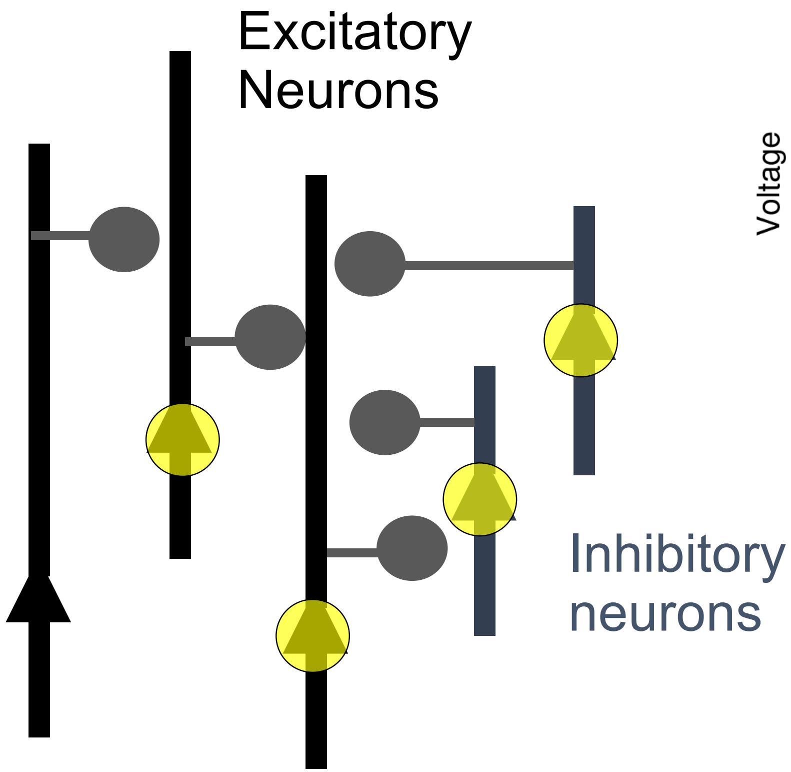

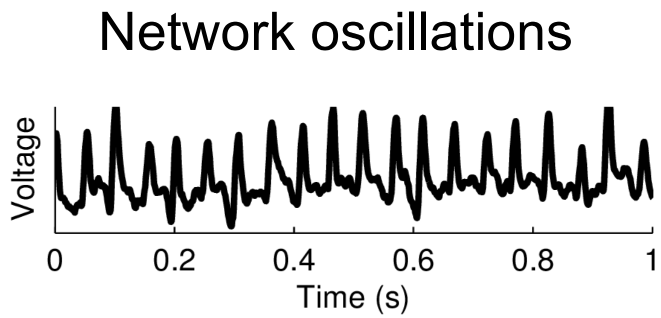

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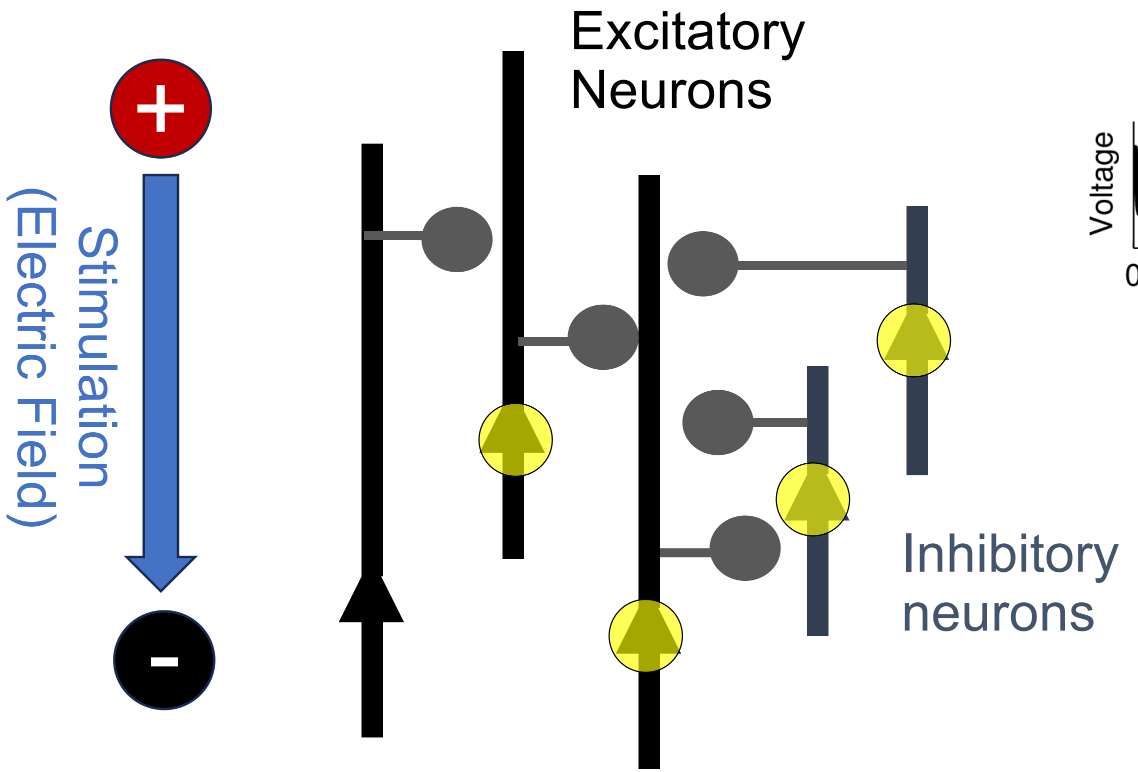

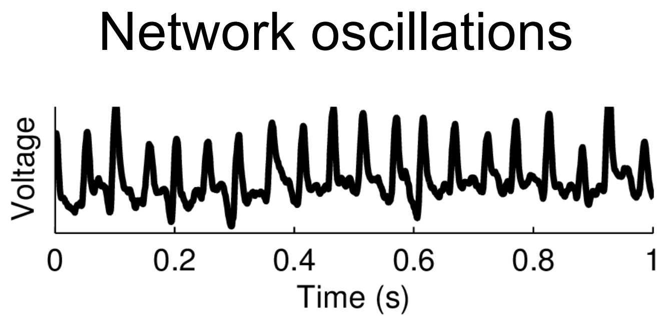

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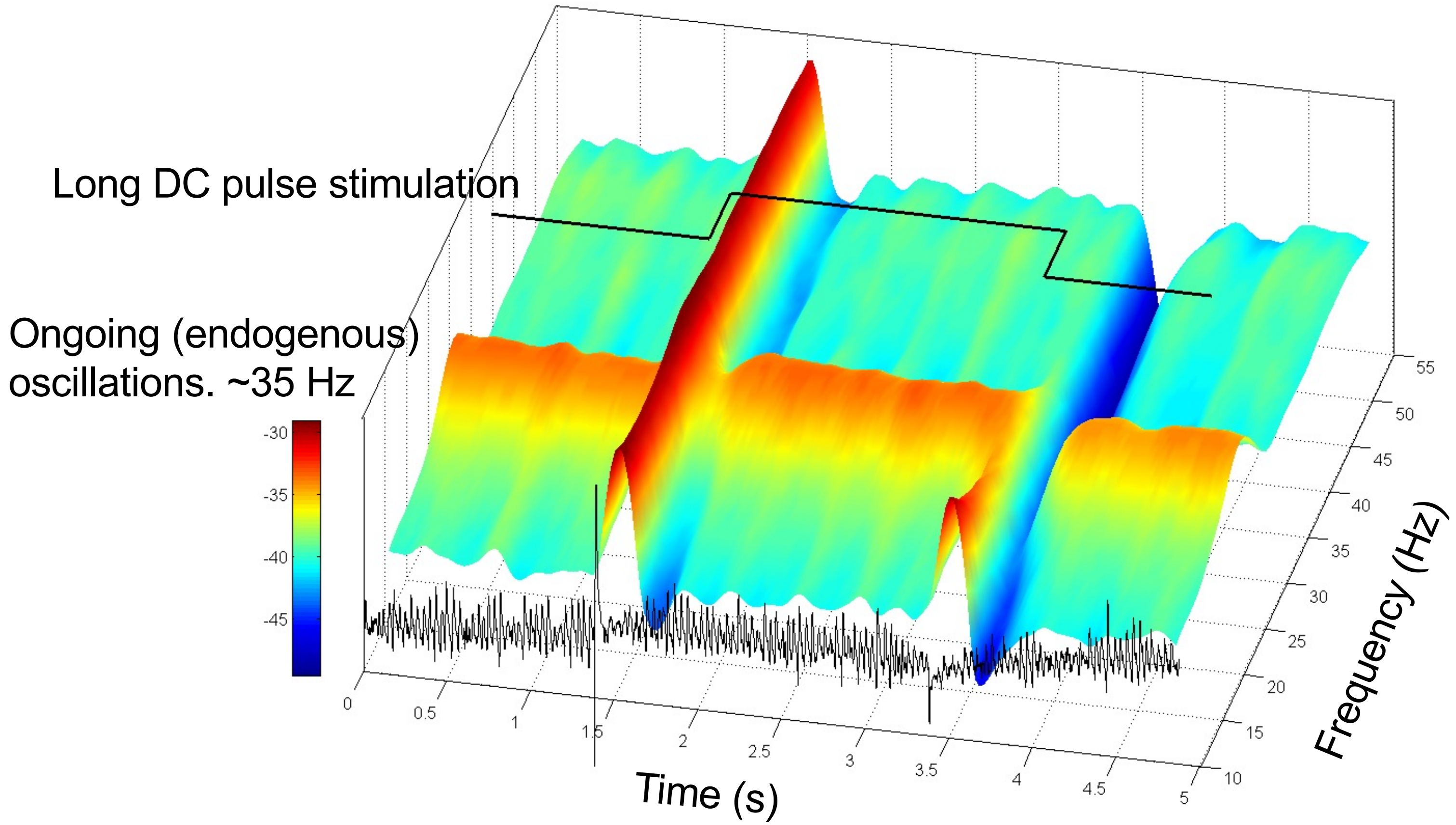
- Oscillating neuronal networks demonstrate high sensitivity to electric fields.
- Network response depend on nature of oscillation and field – are explained with computational models.



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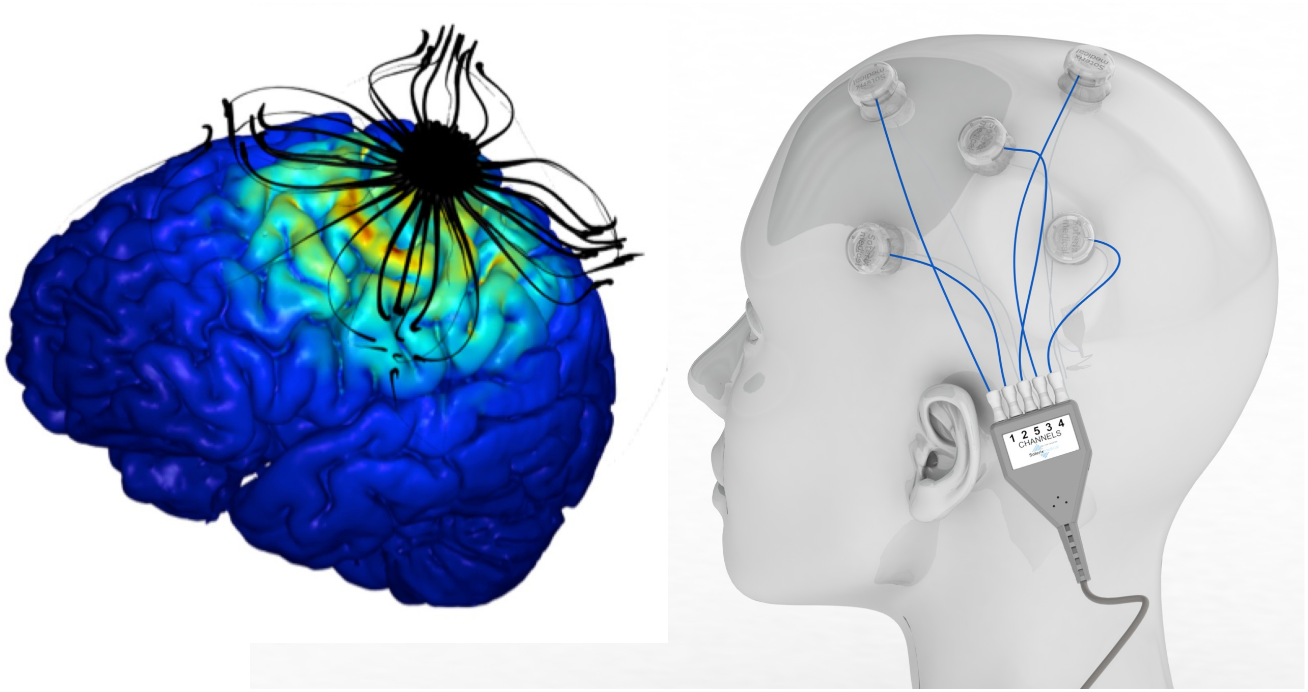
Design of non-invasive electrical brain stimulation

Marom Bikson, **The City College of New York**



Adantchede Louis Zannou, Mojtaba Belali Koochesfahani, Mahima Sharma. Lucas Parra, Marc Russo, Greg Kronberg, Abhishek Datta, Niranjan Khadka, Zeinab Esmaeilpour, Belen Lafon, Mohamad FallahRad, Mark Jackson, Tianhe Zhang, Rosana Esteller, Asif Rahman, Darpan Chakraborty Dennis Truong, Hanoch Kaphzan, Vividha Bhaskar, Thomas Radman