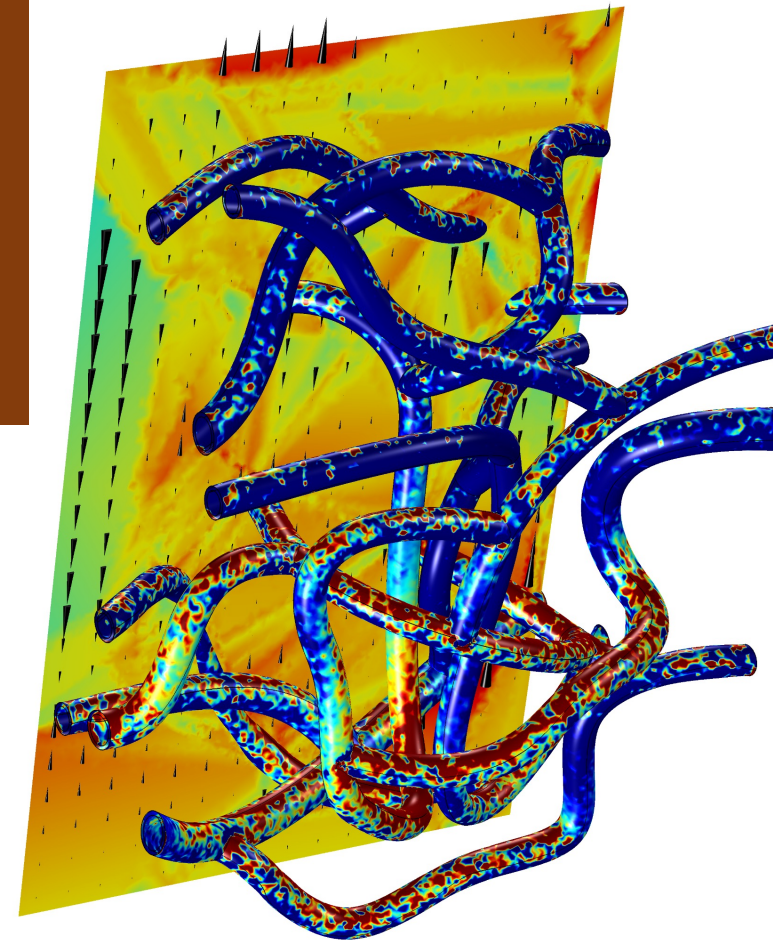


# Neurovascular Modulation: A New Mechanistic Paradigm Linking Diverse Invasive and Non-Invasive Brain Stimulation Approaches (and meditation, yoga, and sleep)

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International Neuromodulation Society (INS) Mumbai, India Nov 11<sup>th</sup> 2022

## **Disclosure**

The City University of New York: Patents on brain stimulation.

Soterix Medical: Produces tDCS and High-Definition tDCS.

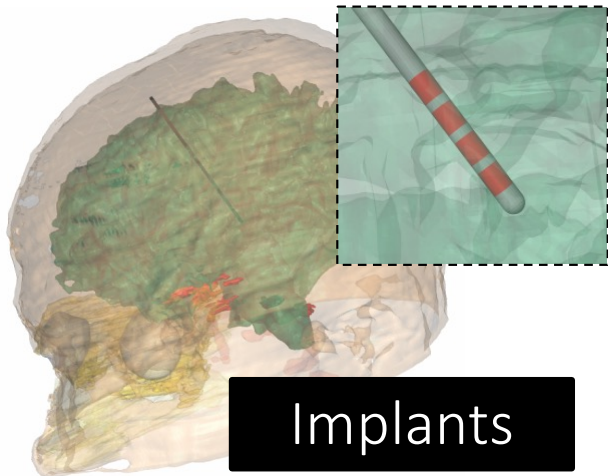
Grants, assigned inventions, and/or serves SAB for SafeToddles, Boston Scientific, GlaxoSmithKline, Biovisics, Mecta, Lumenis, Halo Neuroscience, Google-X, i-Lumen, Humm, Allergan (Abbvie), Apple

## **Support**

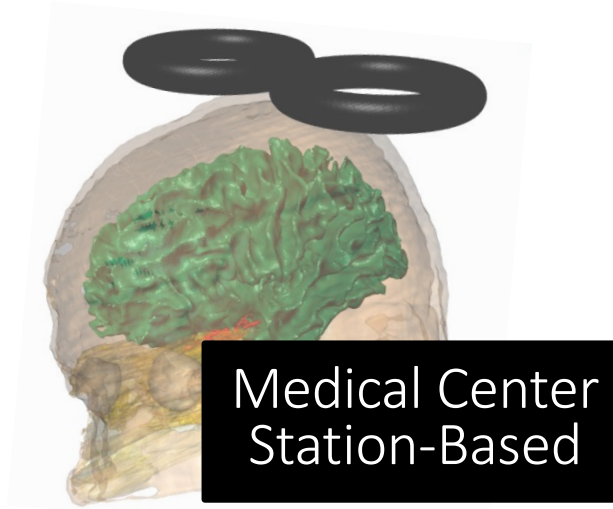
NYS DOH, NIH (NIMH, NINDS) – *BRAIN Initiative*, NSF, Grove Foundation, Harold Shames, CCNY Fund, 21<sup>st</sup> Century Fund



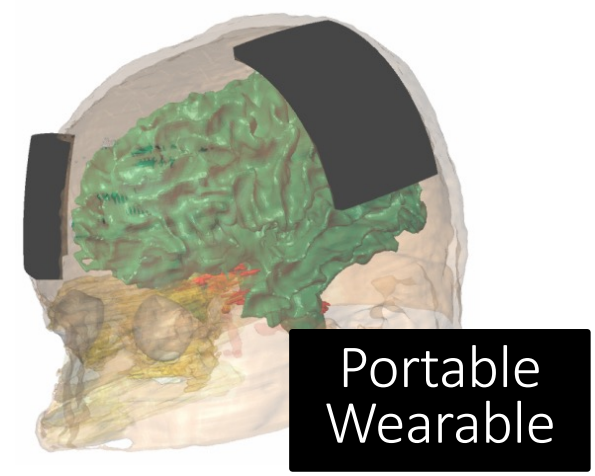
Neuromodulation technologies platforms vary in how energy is delivered to what target.



Deep Brain Stimulation (DBS)  
Spinal Cord Stimulation (SCS)  
Peripheral Nerve Stimulation



Transcranial Magnetic  
Stimulation (TMS)  
Electroconvulsive Therapy  
High-Definition tES (HD-tES)



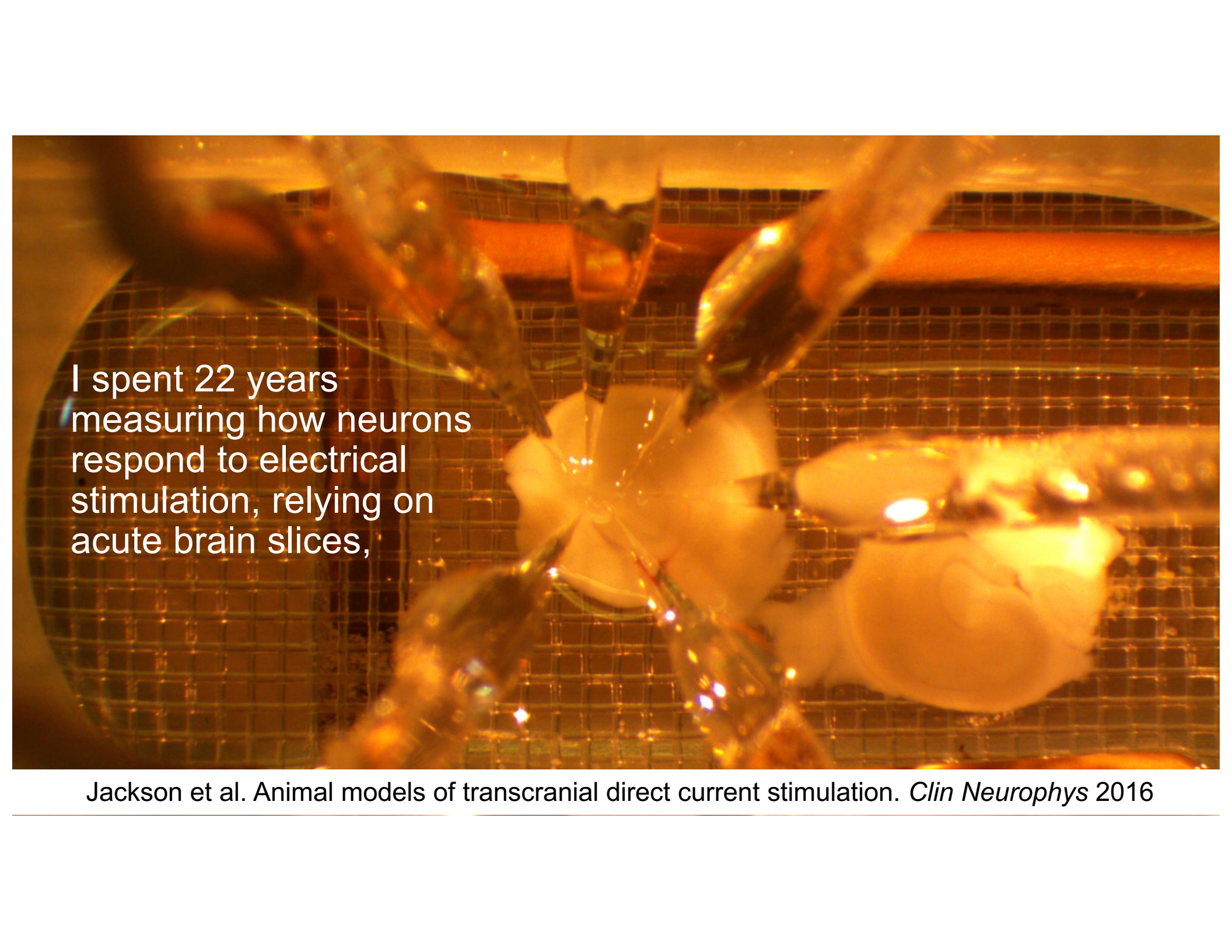
Transcranial Electrical  
Stimulation (tES) / tDCS  
Non-invasive vagus nerve  
simulation / taVNS

Neurovascular-modulation is a mechanism framework applicable to all technologies.  
Mechanically convergent with 'behavioral neuromodulation' (meditation, yoga, sleep).

Decades of rigorous efforts to understand the mechanisms of neuromodulation (across brain disorders) consider which neurons are stimulated.

Which is just fine.





I spent 22 years  
measuring how neurons  
respond to electrical  
stimulation, relying on  
acute brain slices,

Jackson et al. Animal models of transcranial direct current stimulation. *Clin Neurophys* 2016

Decades of rigorous efforts to understand the mechanisms of neuromodulation (across brain disorders) consider which neurons are stimulated.

Which is just fine.

Decades of rigorous efforts to understand the mechanisms of neuromodulation (across brain disorders) consider which neurons are stimulated.

Which is just fine. But....

# **Neurovascular-modulation**

First aspect: Brain stimulation of neuro-vascular coupling.

Second aspect: Direct stimulation of brain vascular/ blood-brain-barrier function.



- **Neurovascular coupling (unit):** Coupling between neuronal activity with vascular flow and blood-brain barrier (BBB) permeability.
- **Two-way interaction.** Neuronal activity activates vascular (eg. fMRI), Transport across BBB tightly controlled to regulate brain function.



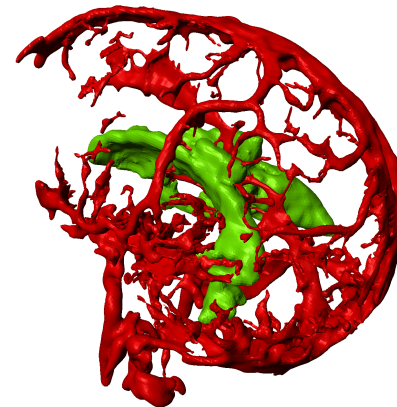
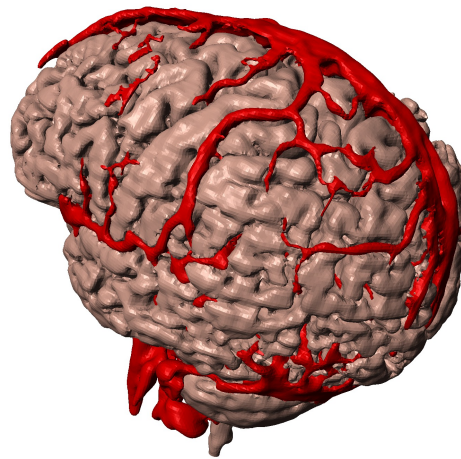
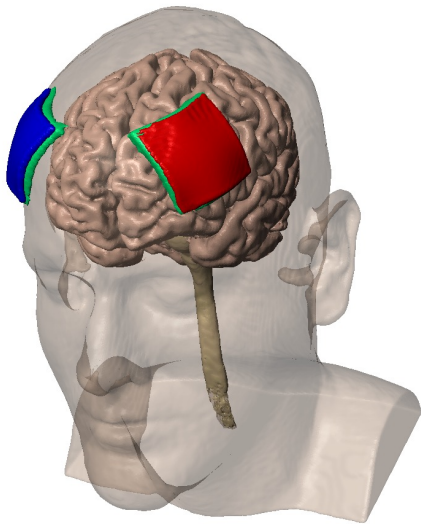
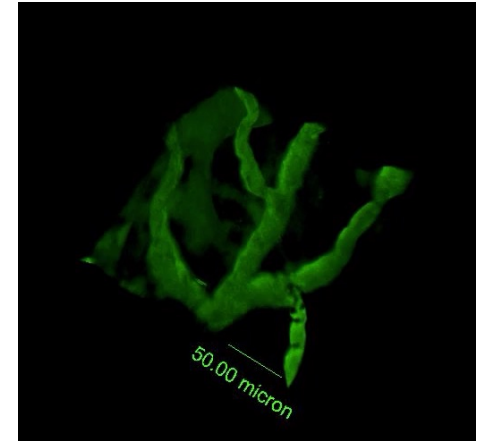
### **Stimulation of neurovascular unit:**

FIRST ASPECT: Brain vasculature changes inevitable **secondary** to neuronal stimulation (eg. fMRI changes after brain stimulation).

SECOND ASPECT: Can neuromodulation **directly** activate endothelial cells of the BBB, leading to secondary neuronal changes.

## Transcranial Direct Current Stimulation (tDCS) of the BBB [second aspect]

Neuronal response to DC fields extensively characterized. Including in brain slices (where vasculature is absent)



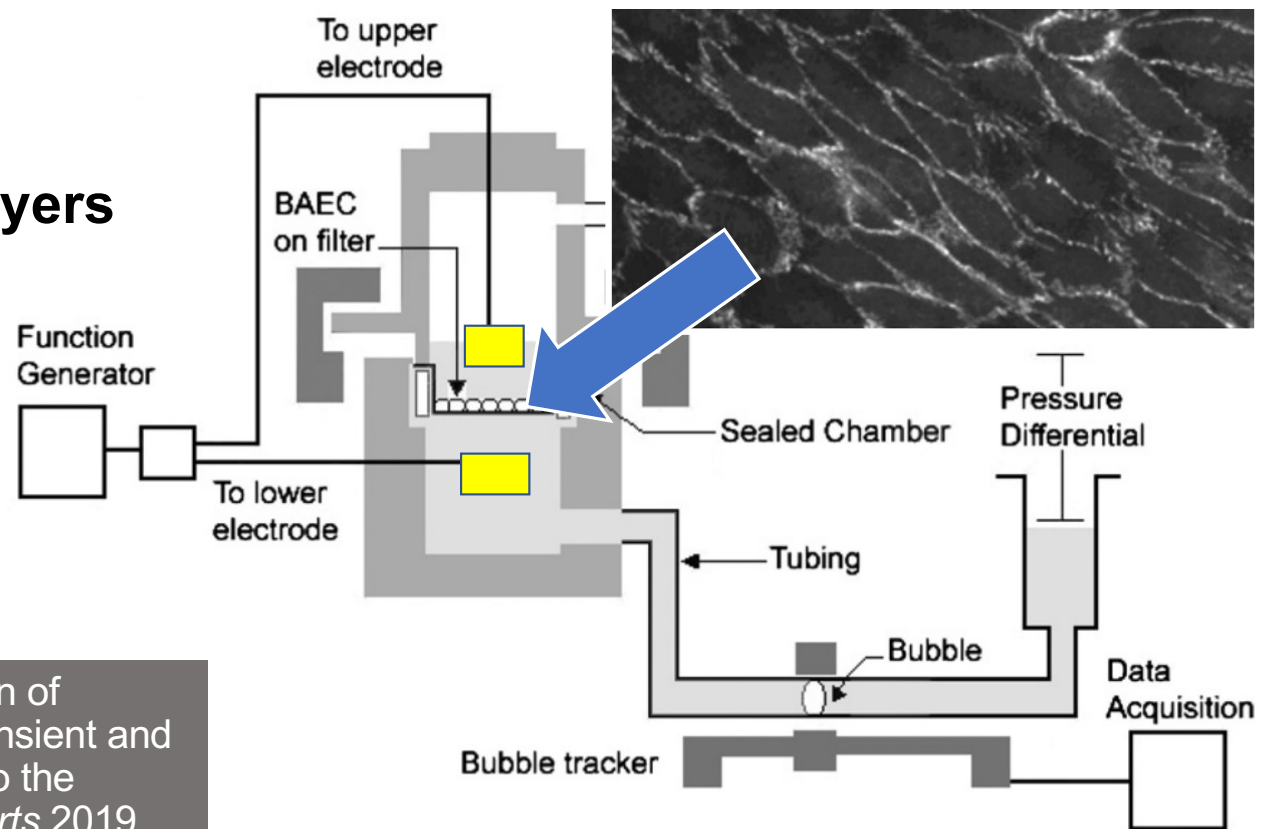
Can tDCS (DC fields) directly activate the BBB, which in turn modulates neurons?

Vascular response to tDCS established (eg. fMRI, fNIRS) but considered epiphenomena !

“Primacy” of neurons as targets of neuromodulation means any changes in vascular function assumed secondary to neuron stimulation.

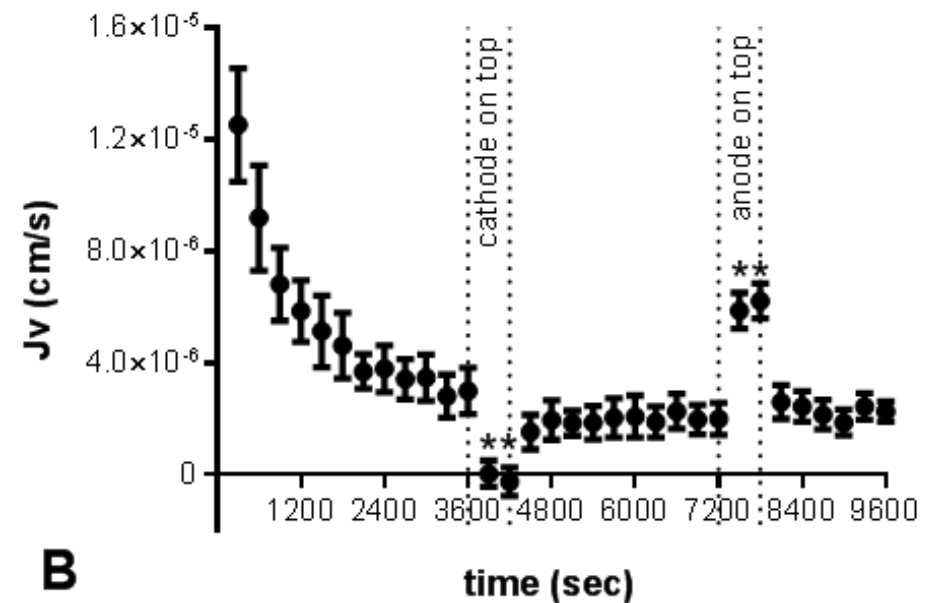
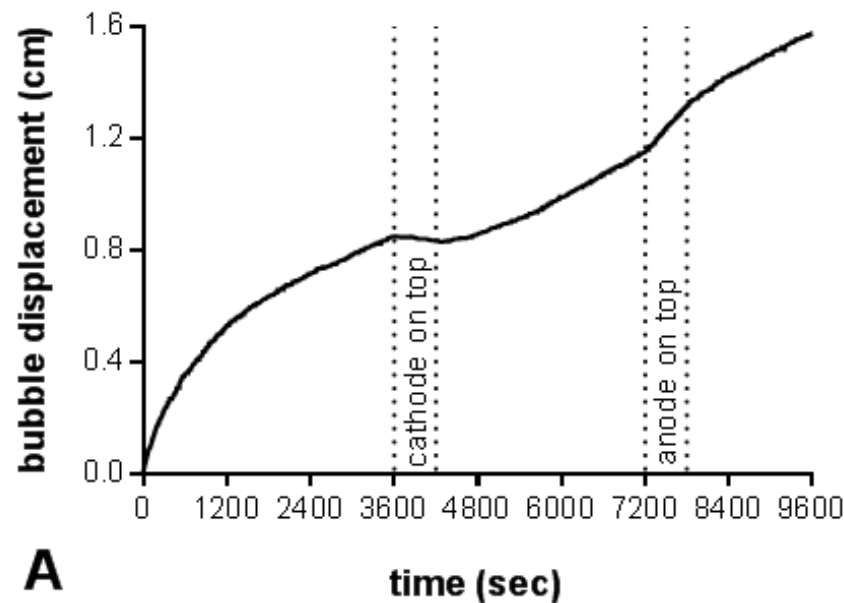
**Isolated BBB stimulation established direct neuromodulation.**

BBB model: **cultured endothelium monolayers**



Cancel et al. Direct current stimulation of endothelial monolayers induces a transient and reversible increase in transport due to the electroosmotic effect. *Scientific Reports* 2019

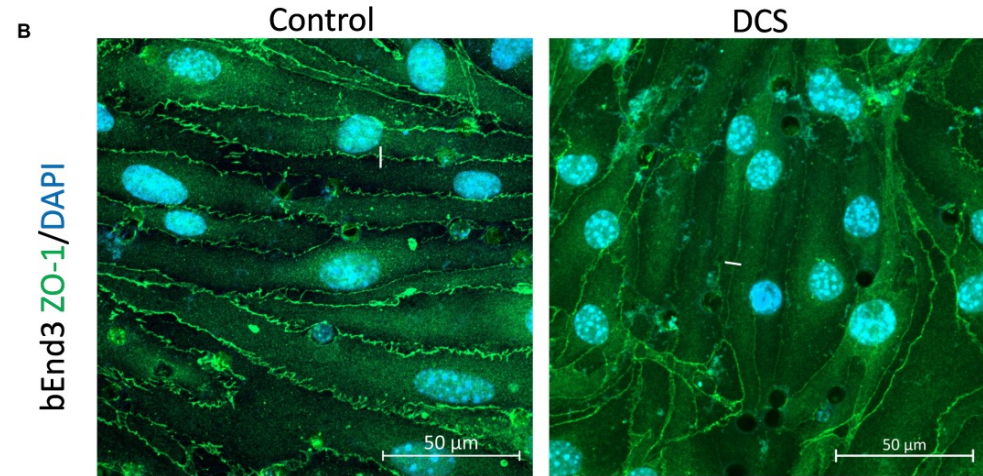
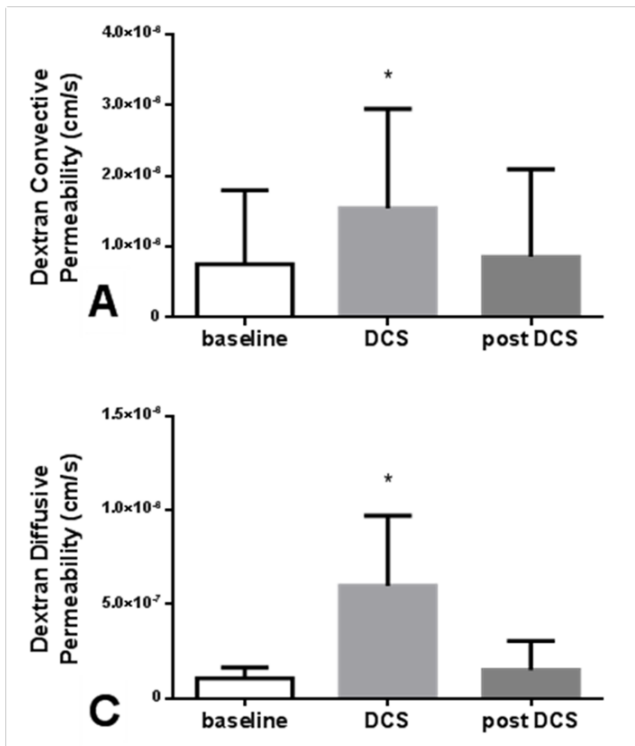
Direct Current stimulation produced an acute, polarity specific change in water transport across BBB model



Electroosmosis: Current will drag water through a (charged) barrier, proportional to tightness of barrier.

Cancel et al. Direct current stimulation of endothelial monolayers induces a transient and reversible increase in transport due to the electroosmotic effect. *Scientific Reports* 2019

Direct Current stimulation enhances specific molecule transport across the BBB and activates structural (tight junction) / molecular (eNOS) / early gene expression (VEGF).

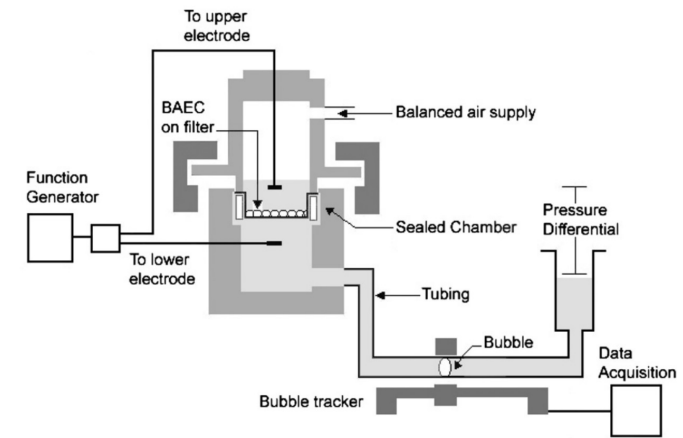
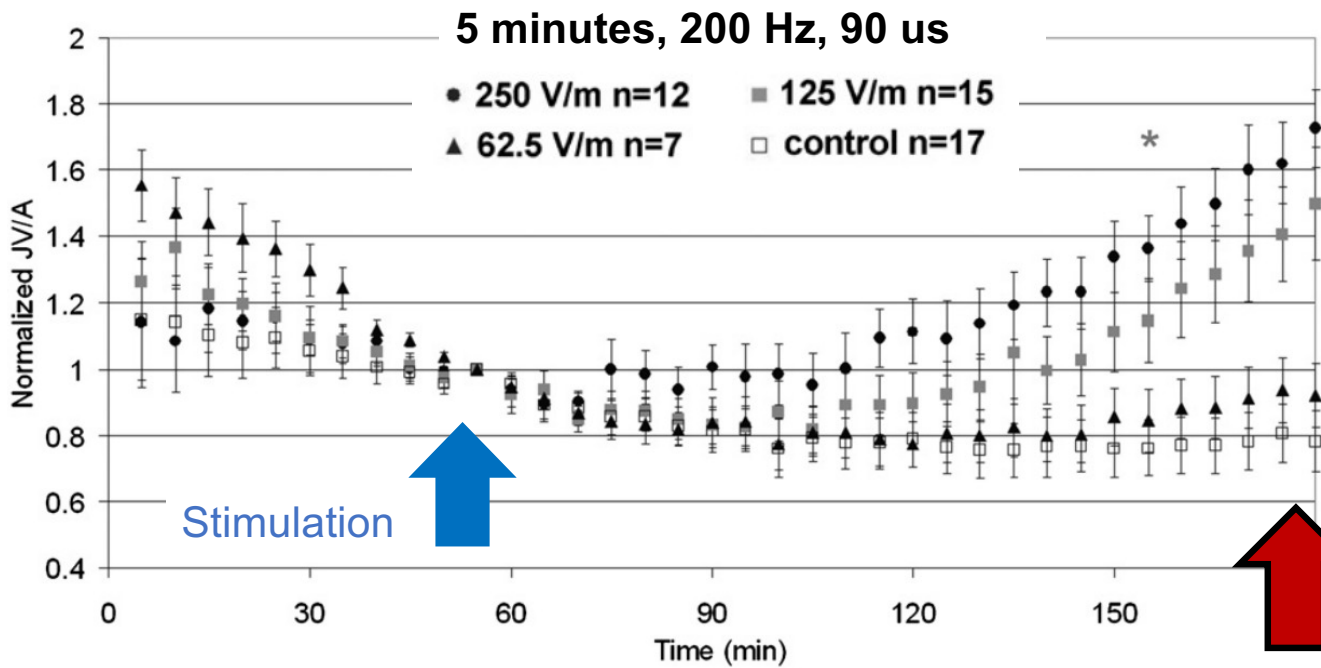


Xia et al. Direct Current Stimulation Disrupts Endothelial Glycocalyx and Tight Junctions of the Blood-Brain Barrier in vitro. *Frontiers cell and developmental biology* 2021

Plasticity from brain vasculature stimulation.

Cancel et al. Direct current stimulation of endothelial monolayers induces a transient and reversible increase in transport due to the electroosmotic effect. *Scientific Reports* 2019

High-intensity pulsed electric fields (DBS, ECT, TMS like) modulate isolated endothelial cells (BBB) including water and transport flux.

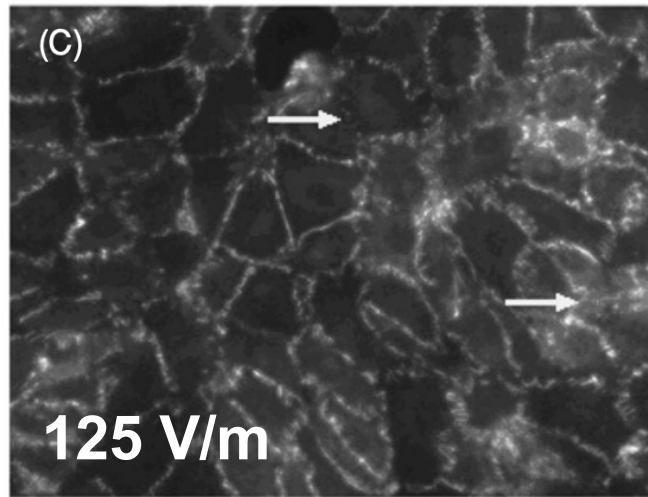
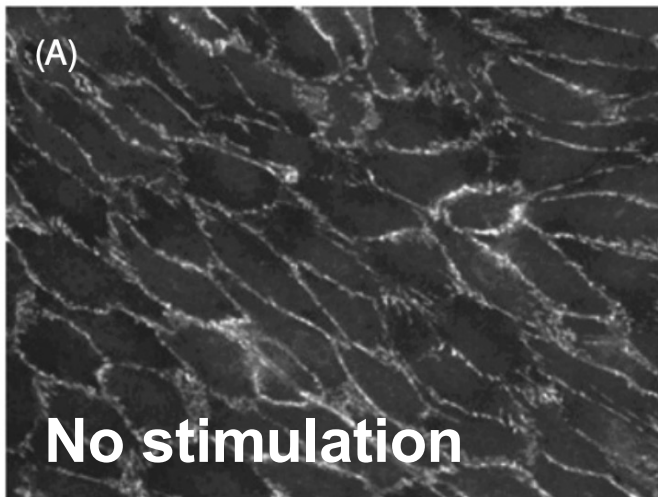


Increased water transport across BBB model following 5 min high-intensity pulsed electric field

Cancel et al. DBS-relevant electric fields increases hydraulic conductivity of in vitro endothelial monolayers. *J Neural Engr* 2010



High-intensity pulsed electric fields (DBS, ECT, TMS like) induce lasting (plastic) changes in endothelial cells (BBB) function.



ZO-1 tight-junction  
protein staining

ZO-1 tight junction protein surrounds endothelial cells in control. Pulses electric fields modify continuity (arrows).

Cancel et al. DBS-relevant electric fields increases hydraulic conductivity of in vitro endothelial monolayers. *J Neural Engr* 2010

## Neurovascular Modulation: Direct effects on brain vasculature suggest unique therapeutic strategies (pathways)

### ”Boosting” of brain function (transport) / neurorehabilitation efficacy

- Cancel et al. DCS of endothelial monolayers induces a transient and reversible increase in transport due to electroosmotic. *Sci Reports* 2019
- Shin et al. In Vivo Modulation of the Blood-Brain Barrier Permeability by tDCS. *Ann Biomed Eng.* 2020

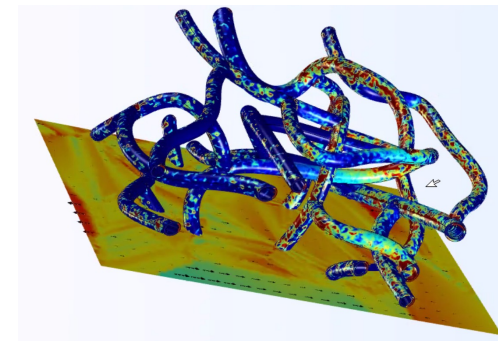
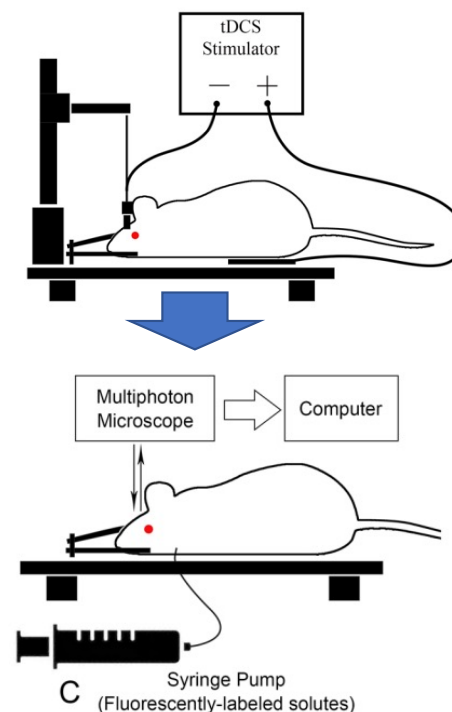
### Drive brain clearance (eg. dementia)

- Khadka et al. Neurocapillary-modulation. *Neuromodulation.* 2020
- Xia et. al Modulation of solute diffusivity in brain tissue as a novel mechanism of transcranial direct current stimulation (tDCS). *Sci Rep* 2020

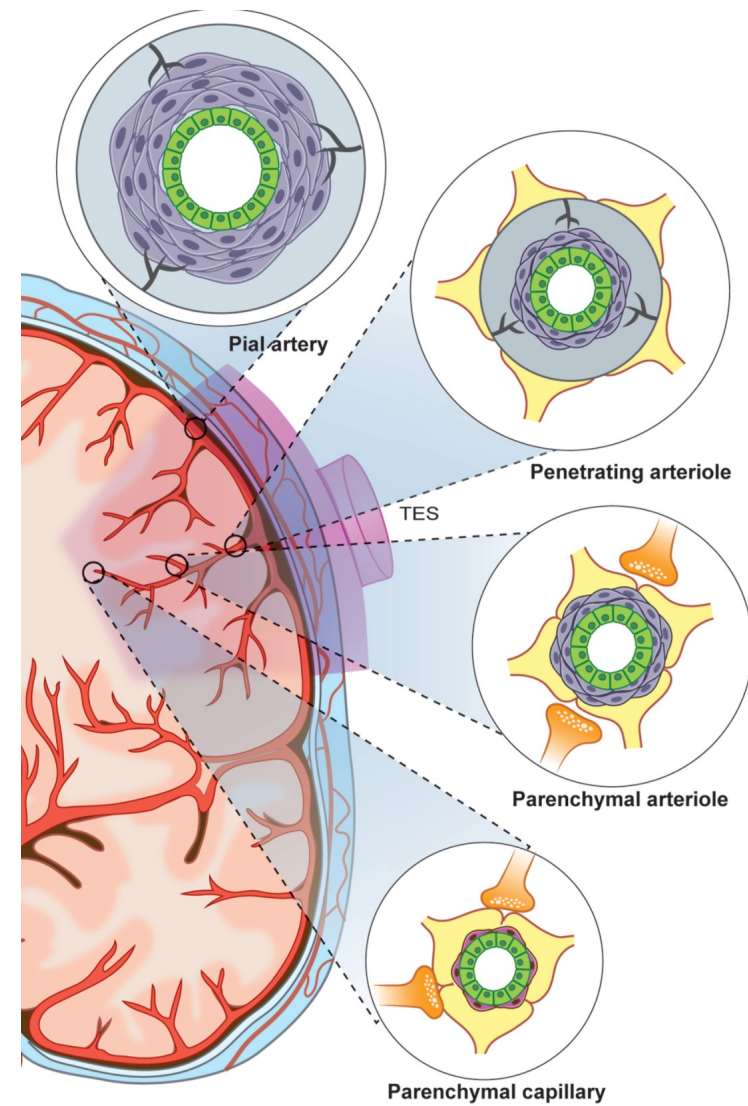
Convergent with therapy mechanism of meditation, yoga, sleep.

### Neuro-protective role (acute stroke)

- Bahr Hosseini et al. CNS Electrical Stimulation for Neuroprotection in Acute Cerebral Ischemia: Meta-Analysis of Preclinical Studies. *Stroke* 2019



# Why neurovascular modulation?



Bahr-Hosseini et al. Neurovascular-modulation. *Brain Stim* 2021

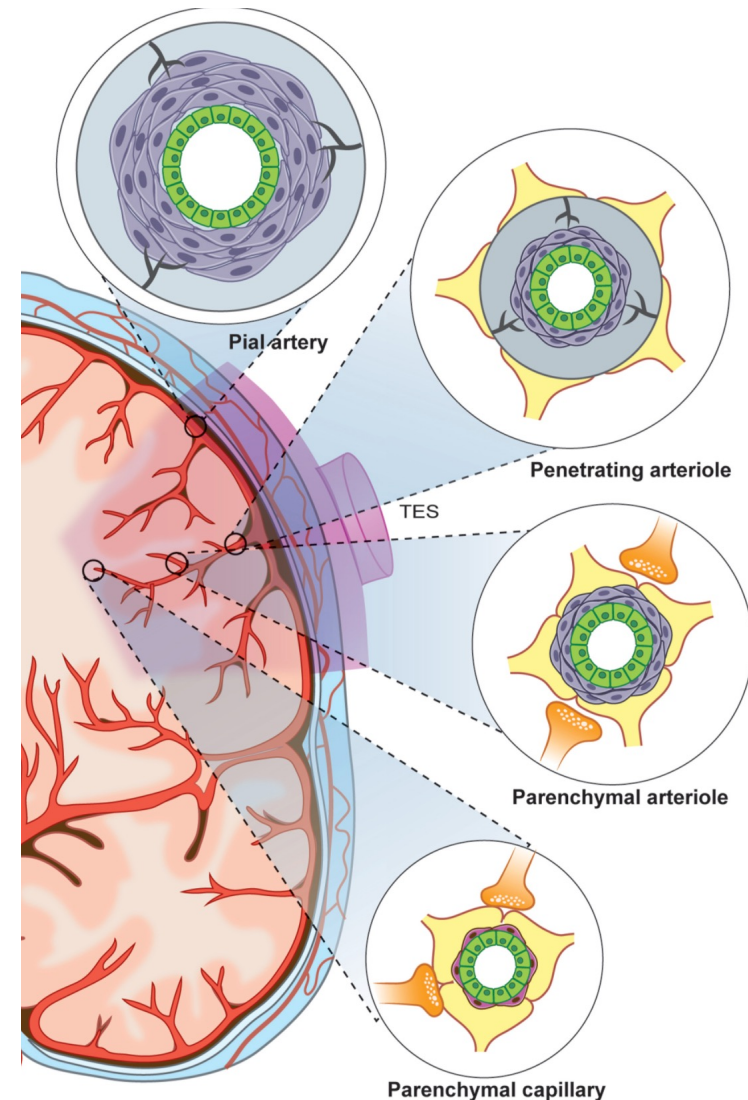
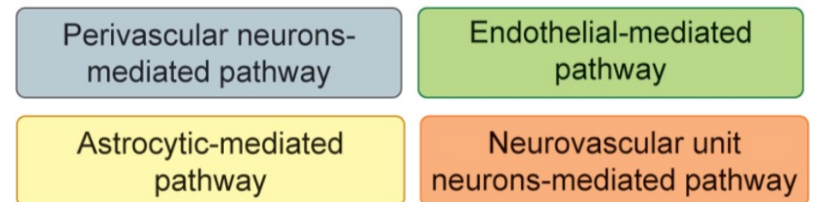
# Why neurovascular modulation?

- Neurons are not alone in the brain. And are not functional without cells supporting transport.



FIRST ASPECT: Neuronal stimulation must consider neurovascular coupling.

SECOND ASPECT: Direct stimulation of brain vasculature.



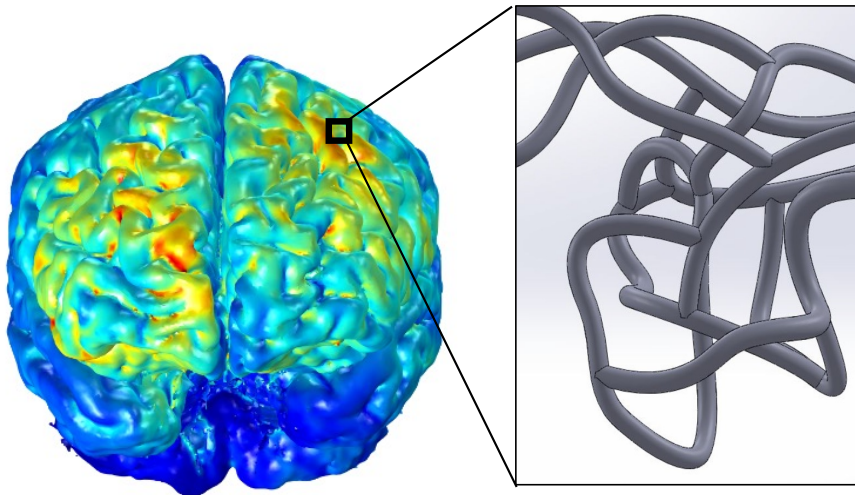
# **Neurocapillary-modulation**

Second aspect: Direct stimulation of brain vascular/ blood-brain-barrier function.



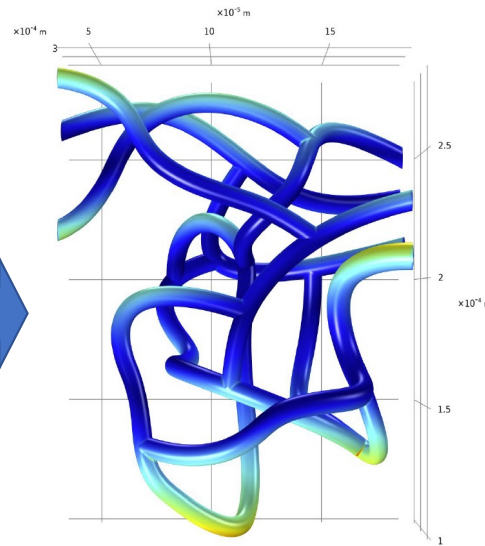
# Neurovascular modulation

Macroscale (anatomy based) current flow models.  
Brain parenchyma Electric Field :  
(0.4 V/m at 1 mA tDCS)



Multi-scale models with brain vasculature structure.

Microscale current flow models. BBB Electric Field :  
(160 V/m at 1 mA tDCS)



The structure of capillaries (extremely resistive wall, conductive interior) change microscopic current flow.

Electric fields are magnified across the Blood-Brain-Barrier (>400x of brain parenchyma).

For DBS /SCS /TMS/ ECT/ VNS: BBB Electric Fields >10,000 V/m

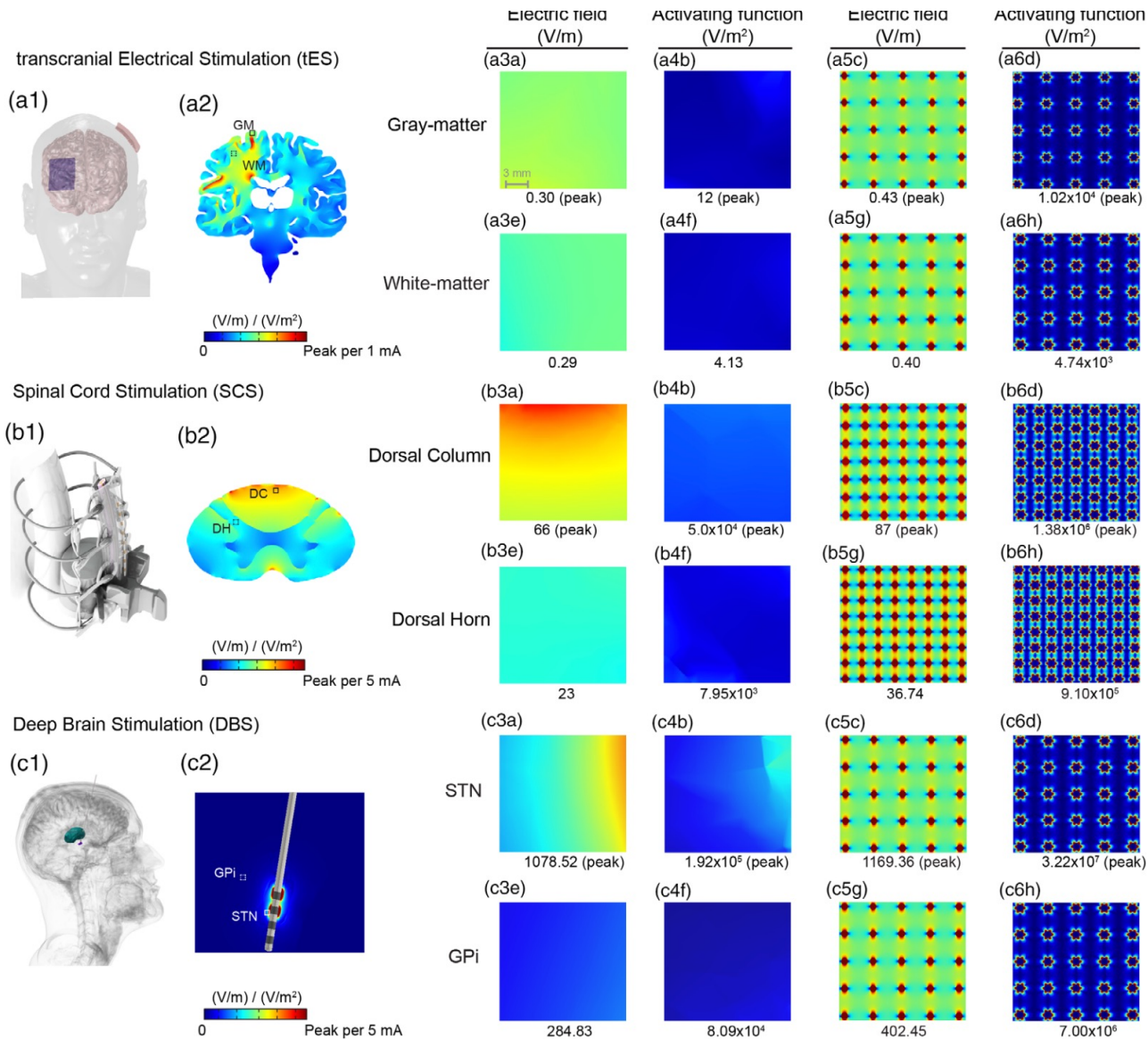
Multi-physics models couple to treatment mechanisms (eg. fluid clearance).



# Neurocapillary-modulation

Third aspect: Fundamentally changing how neurons are directly stimulated

.



Application of neurocapillary-modulation in tES, DBS, and SCS. Degree and spatial extent of electrical current flow distortion in the brain parenchyma around brain capillaries and the resulting amplification of neuronal polarization, driving factors such as electric field and activating function

Khadka et al. Neurocapillary-modulation. Neuromodulation: Technology at the Neural Interface. 2020

## Things **Neuro-vascular Modulation** can explain

FIRST ASPECT: Brain stimulation (tDCS, TMS, ECT, DBS....) cannot significantly modulate neuronal function without engaging neuro-vascular coupling.

Imaging by hemodynamic coupling (fMRI...) **measure changes in neuro-vascular coupling.**



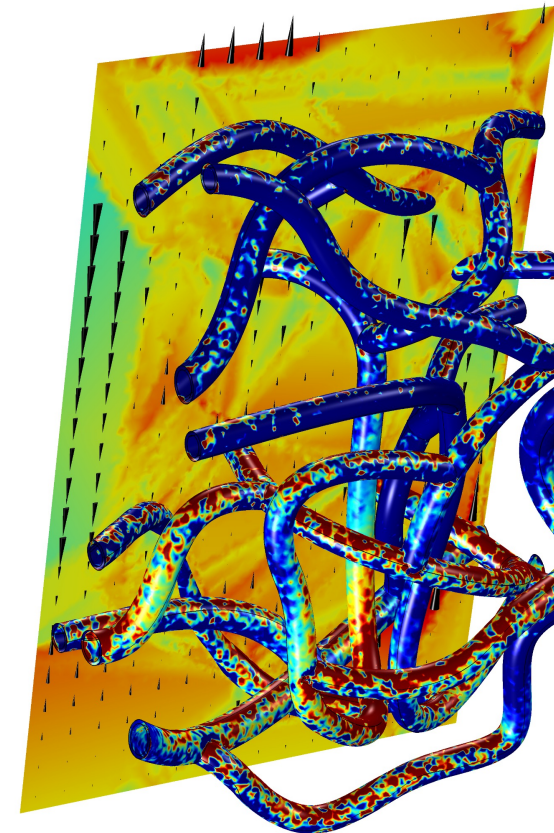
SECOND ASPECT: Direct vascular (BBB) stimulation plausible - in a dose / mechanisms / time-course specific manner.

Specific system / behavioral scale outcomes. And suggests **unique therapy strategies** (brain “flushing...”)

Convergent (synergistic) mechanisms with meditation, yoga, sleep...



THIRD ASPECT: Reconsider how neuronal compartments or polarized. Impacts **neuronal sensitivity** (can provide “super-sensitivity” above traditional theory) and spatial distribution.



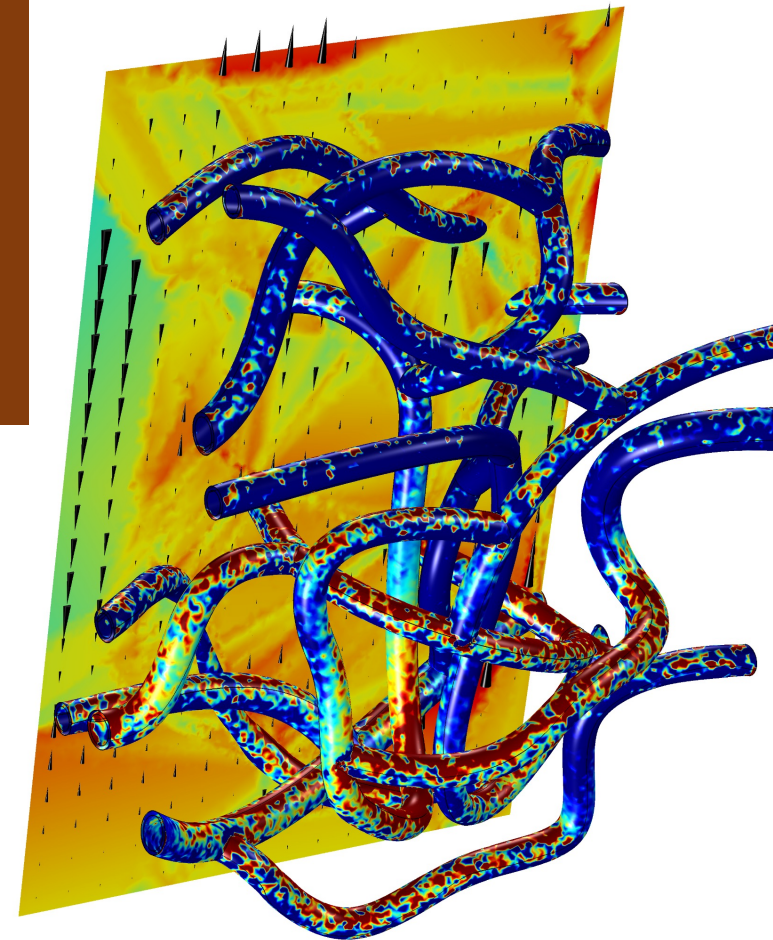
Multi-scale multi-physics model predict fluid “push” around brain during stimulation.

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