Neuro-vascular Modulation and Brain Response to Transcranial Electrical Stimulation

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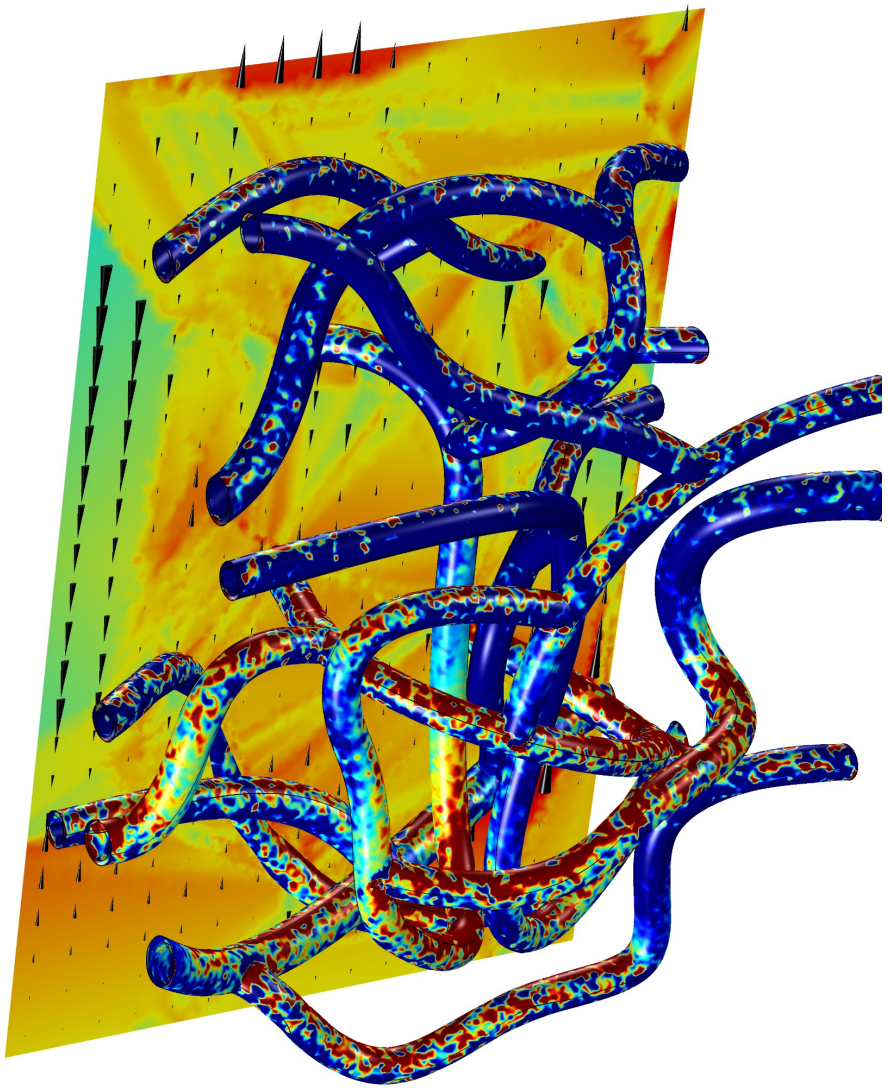


International Brain Stimulation Conference, 2023 ON DEMAND SYMPOSIUM

Disclosure

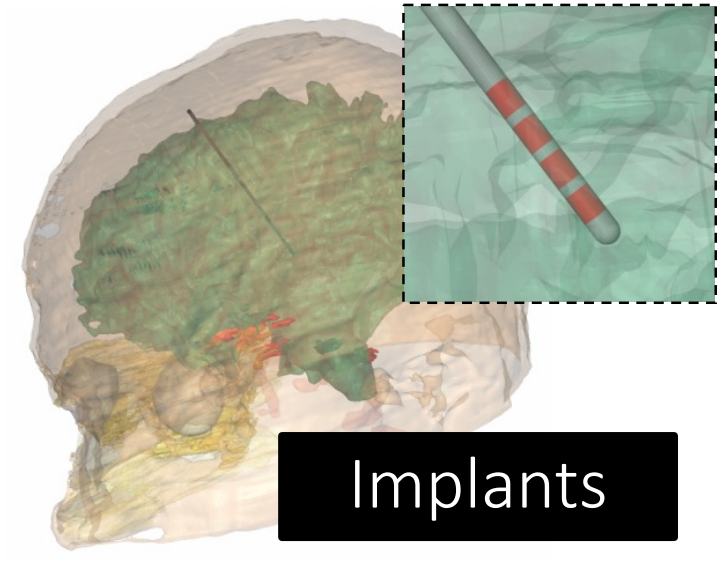
The City University of New York: Patents on brain stimulation.
Soterix Medical: Produces tDCS and High-Definition tDCS.
Grants, assigned inventions, and/or serves SAB for SafeToddles, Boston Scientific, GlaxoSmithKline, Biovisics, Mecta, Lumenis, Halo Neuroscience, Google-X, i-Lumen, Humm, Allergan (Abbvie), Apple

Support

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

Slides and References @MaromBikson

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

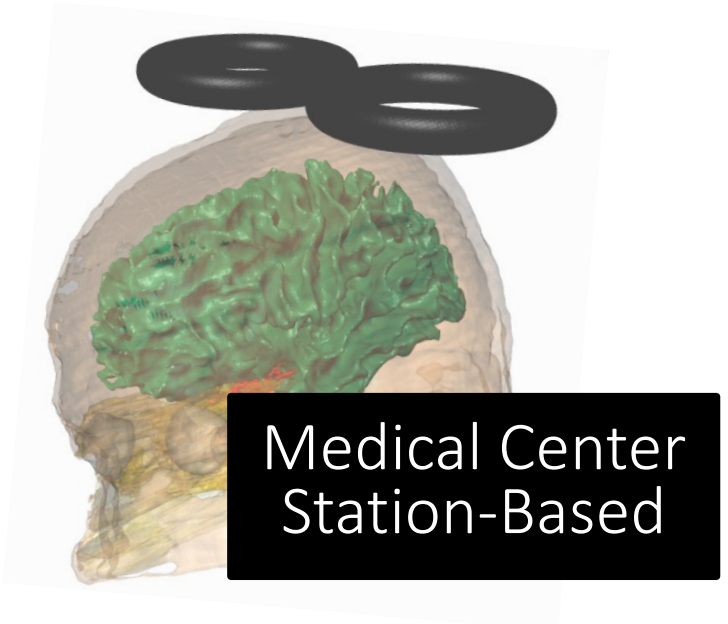


Implants

Deep Brain Stimulation (DBS)

Spinal Cord Stimulation (SCS)

Peripheral Nerve Stimulation

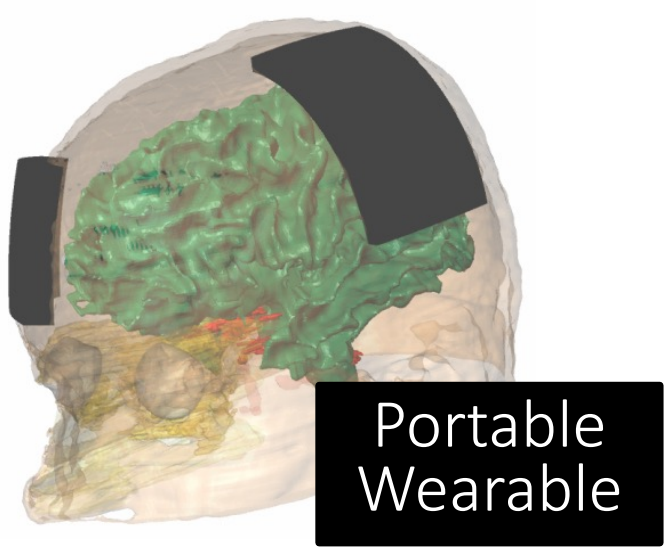


Medical Center Station-Based

Transcranial Magnetic Stimulation (TMS / rTMS)

Electroconvulsive Therapy

High-Definition tES (HD-tES)



Portable Wearable

Transcranial Electrical Stimulation (tES) / tDCS

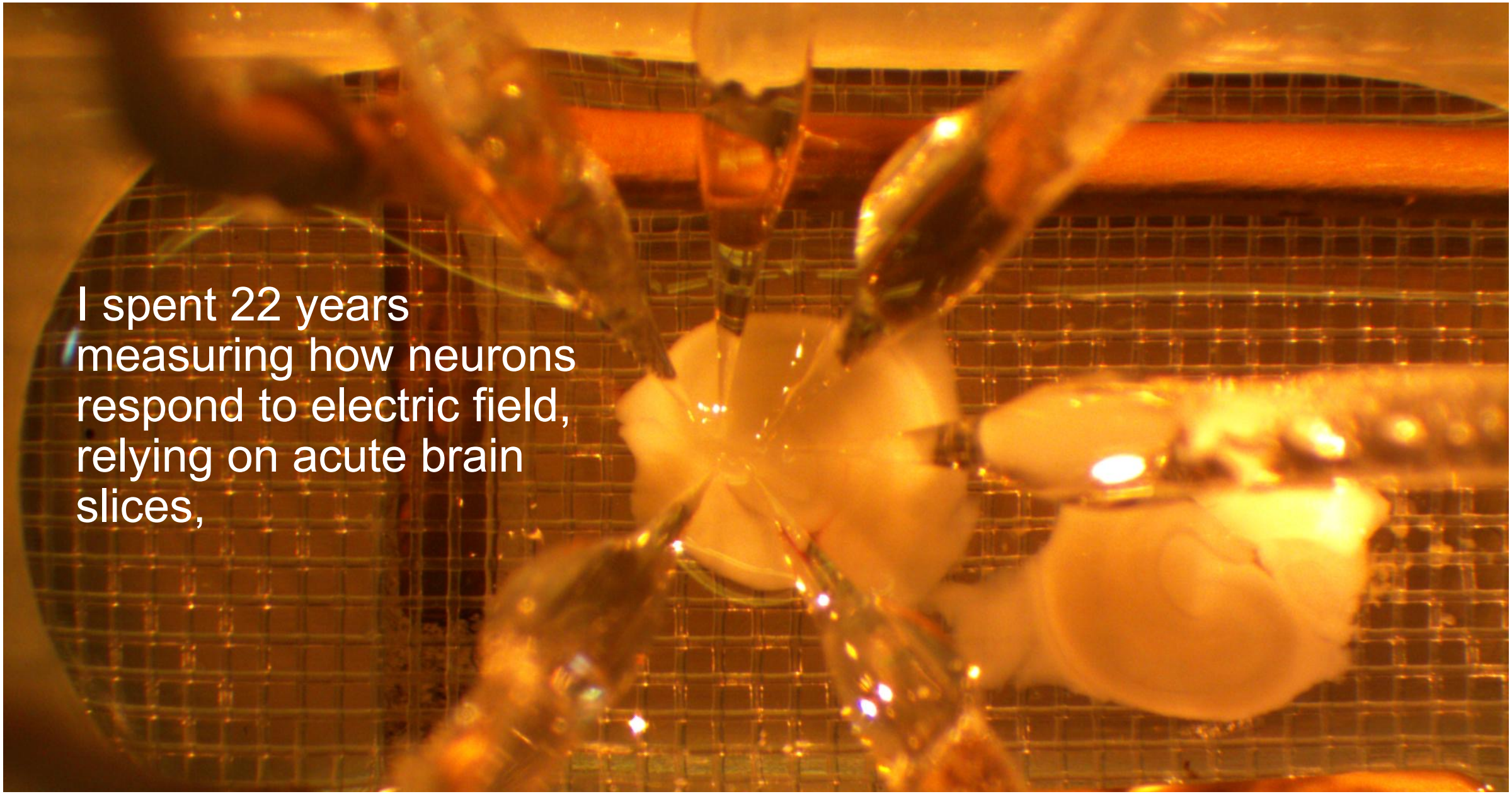
Non-invasive vagus nerve simulation / taVNS

Currents (electric fields) are generated across brain tissue, changing brain function.

Neurovascular-modulation is a mechanism framework applicable to all technologies.

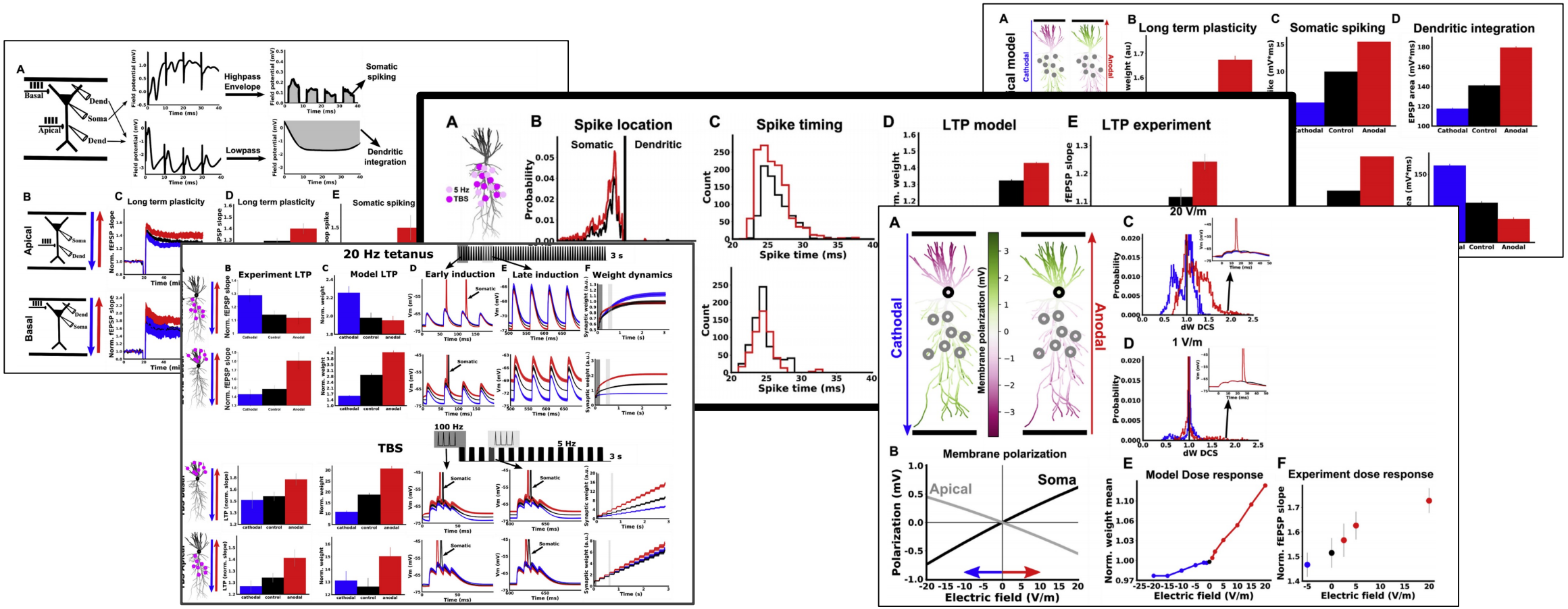
Decades of rigorous efforts to understand the mechanisms of neuromodulation (across brain disorders) consider how neurons are stimulated.

Which is just fine.



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

Well established: Electric fields “directly” modulate neuronal oscillations, neuronal processing, and neuronal plasticity



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

Kronberg et al. Direct current stimulation boosts Hebbian plasticity in vitro. *Brain Stim* 2020

Reato et al. Effects of weak transcranial alternating current stimulation on brain activity. *Frontiers* 2013

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

Which is just fine.

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

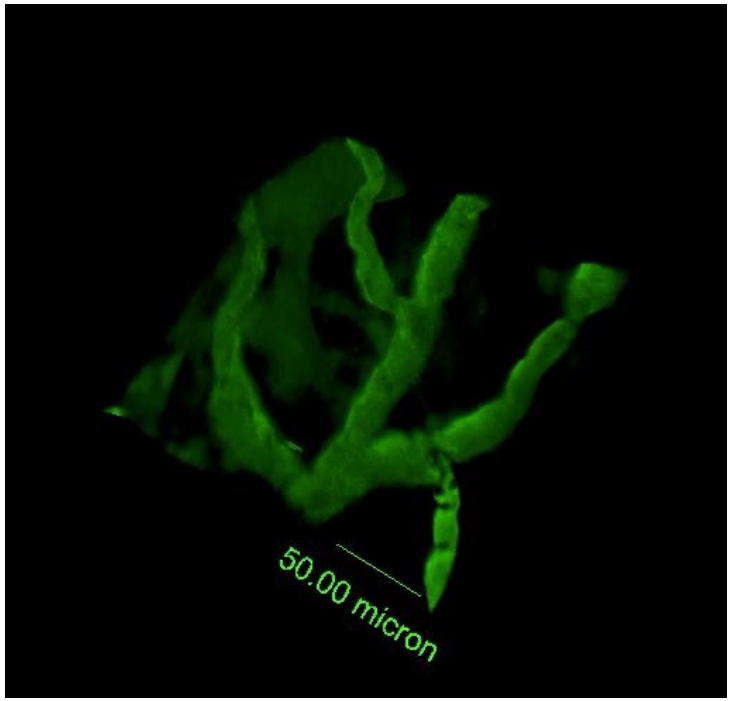
Which is just fine. But….

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.

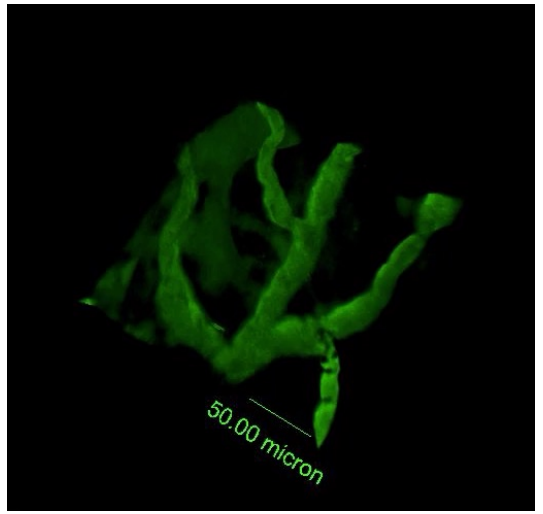


Stimulation of neurovascular unit:

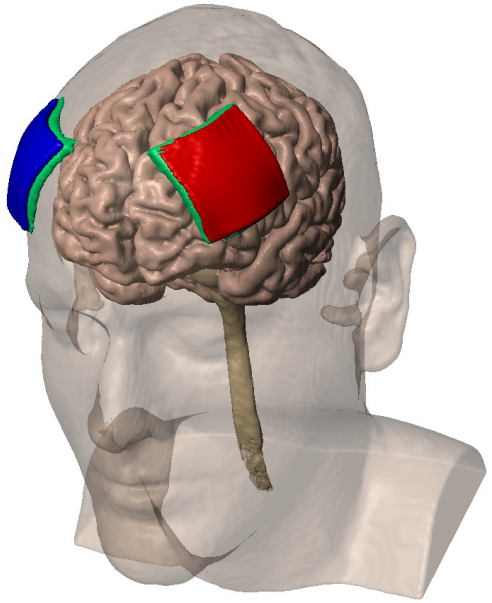
FIRST ASPECT: Brain vasculature changes inevitable **secondary** to neuronal stimulation (eg. fMRI of brain stimulation) and explanatory of outcome.

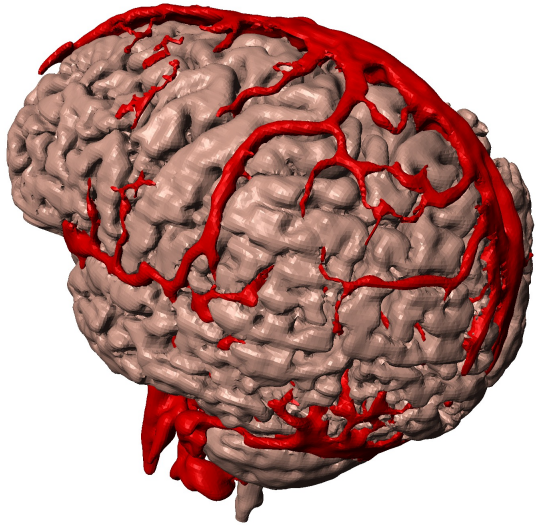
SECOND ASPECT: Neuromodulation **directly** stimulates endothelial cells / glia, modulating brain transport mechanisms (cerebral blood flow, BBB), leading to secondary neuronal changes.

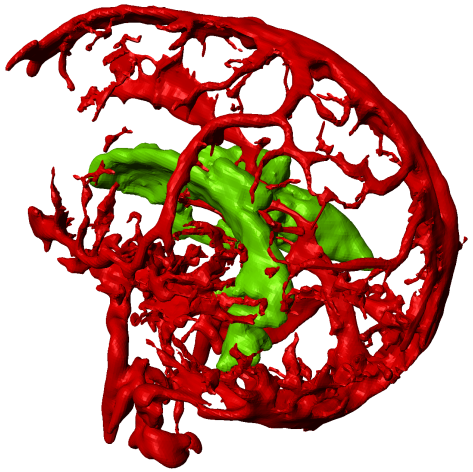
Transcranial Direct Current Stimulation (tDCS) of the BBB [second aspect]



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







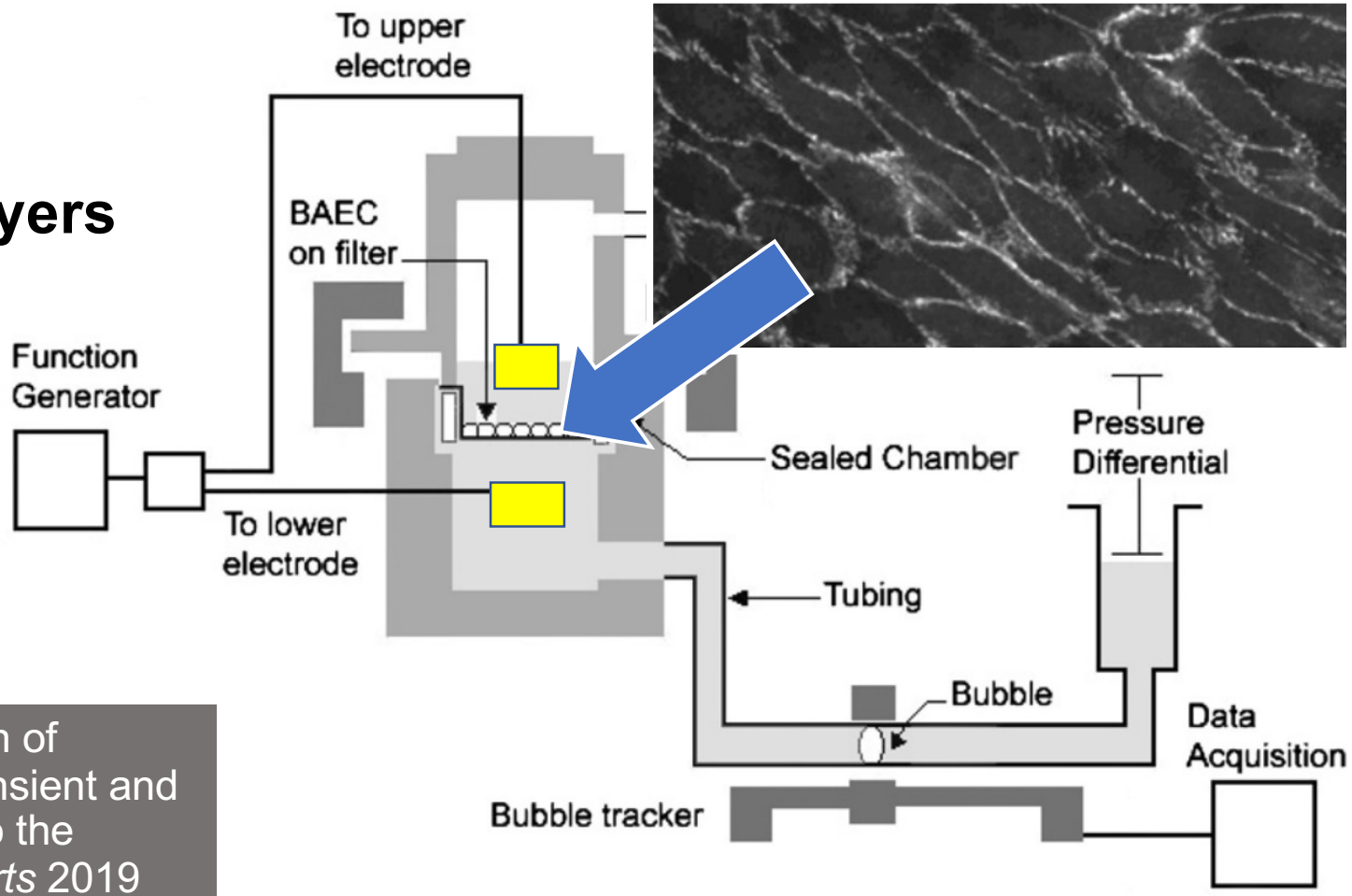
Can tDCS (DC fields) directly activate the BBB, which in turn modulates neurons?

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.

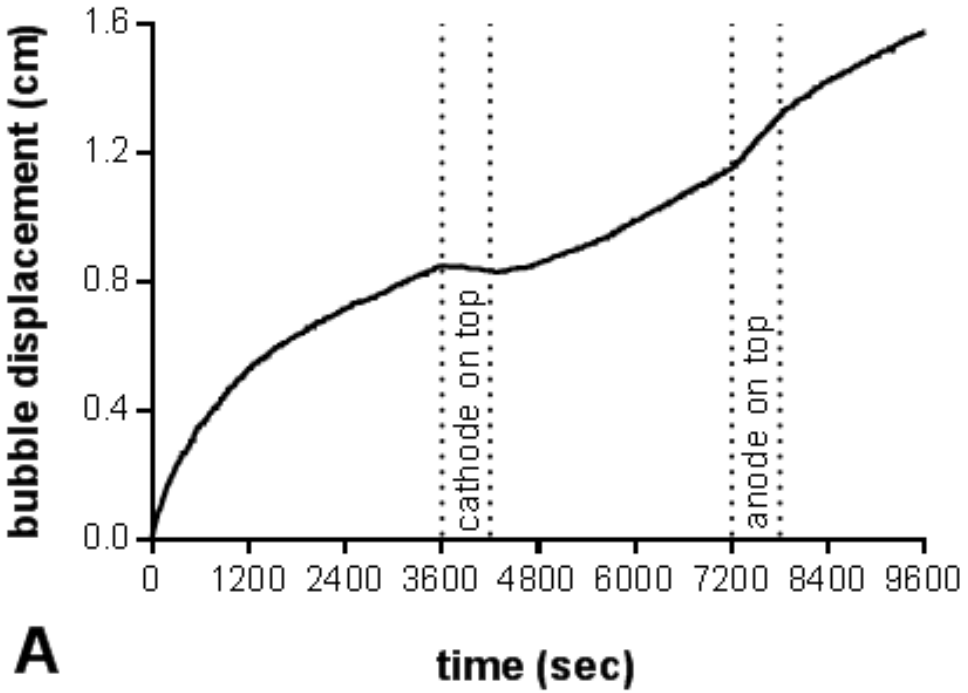
Isolated BBB stimulation established direct neuromodulation.

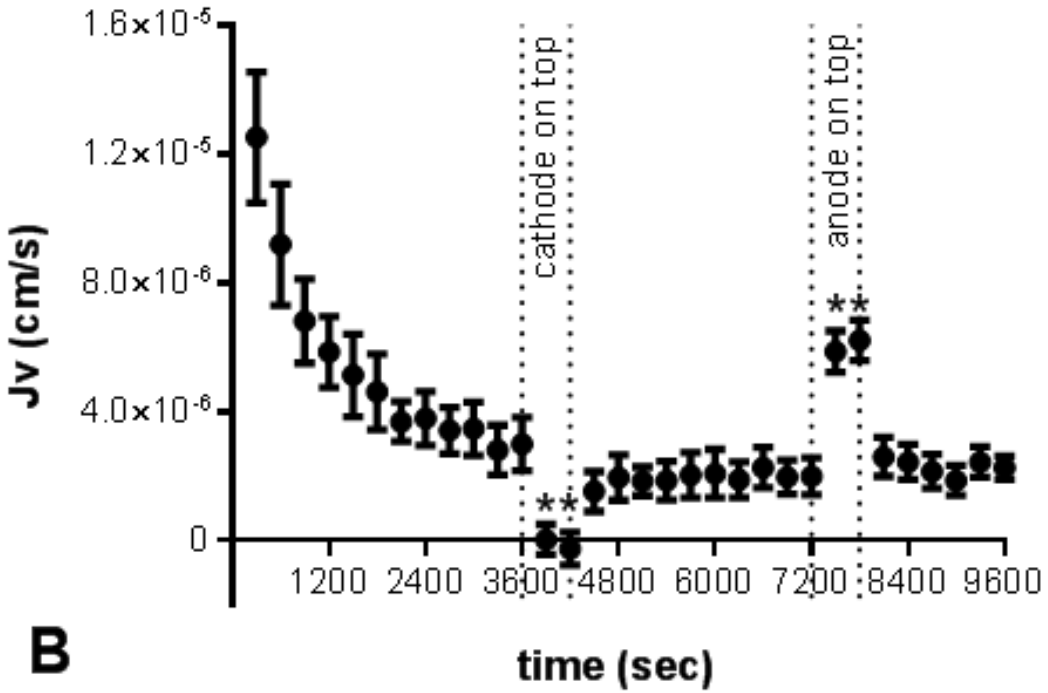
BBB model: **cultured endothelium monolayers**



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

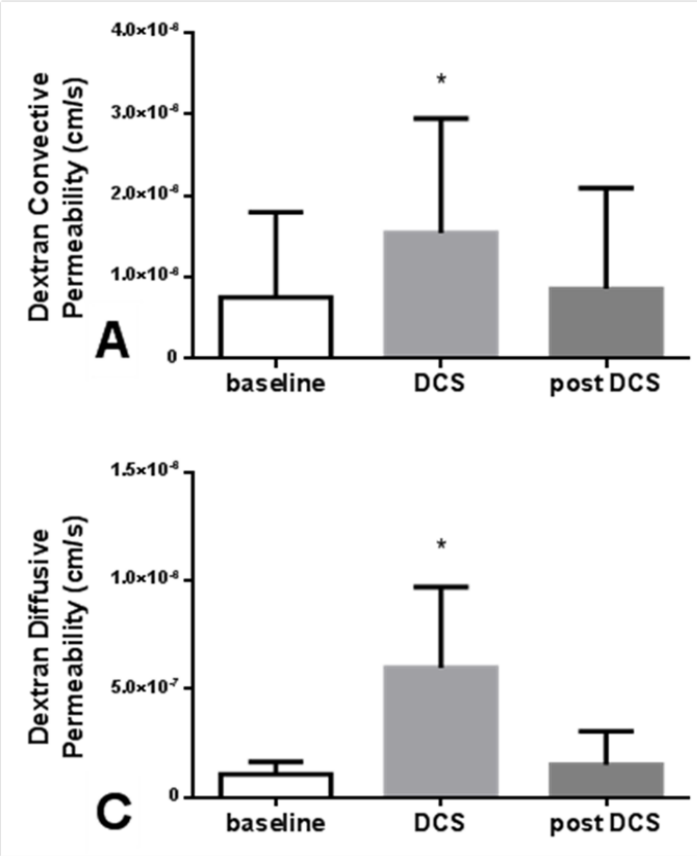


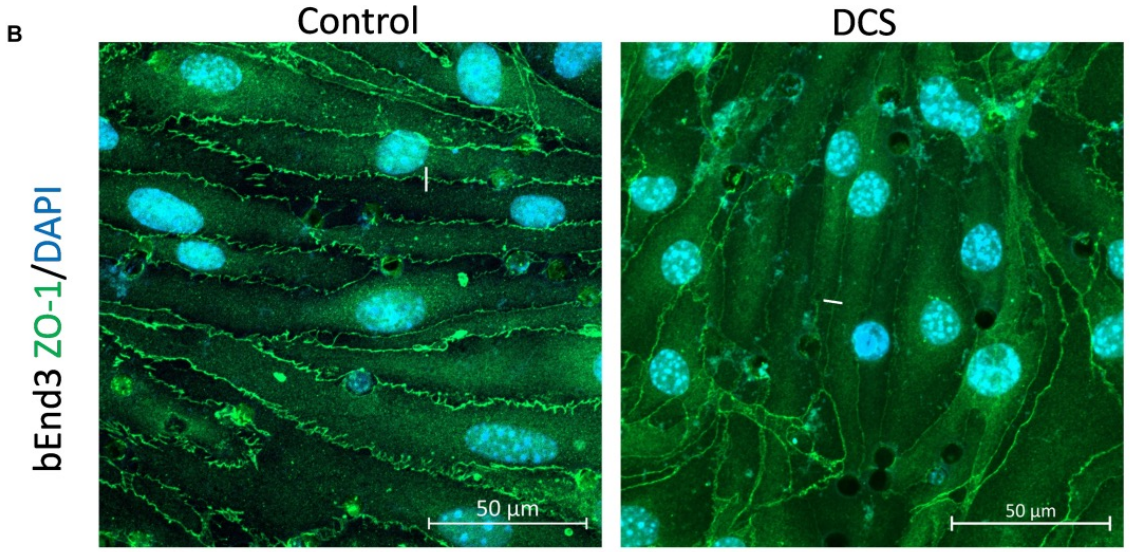


Electroosmosis: Current will drag water through a (charged) barrier, proportional to tightness of barrier.

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 BBB / activates structural (tight junction) / molecular (eNOS) / early gene expression (VEGF).





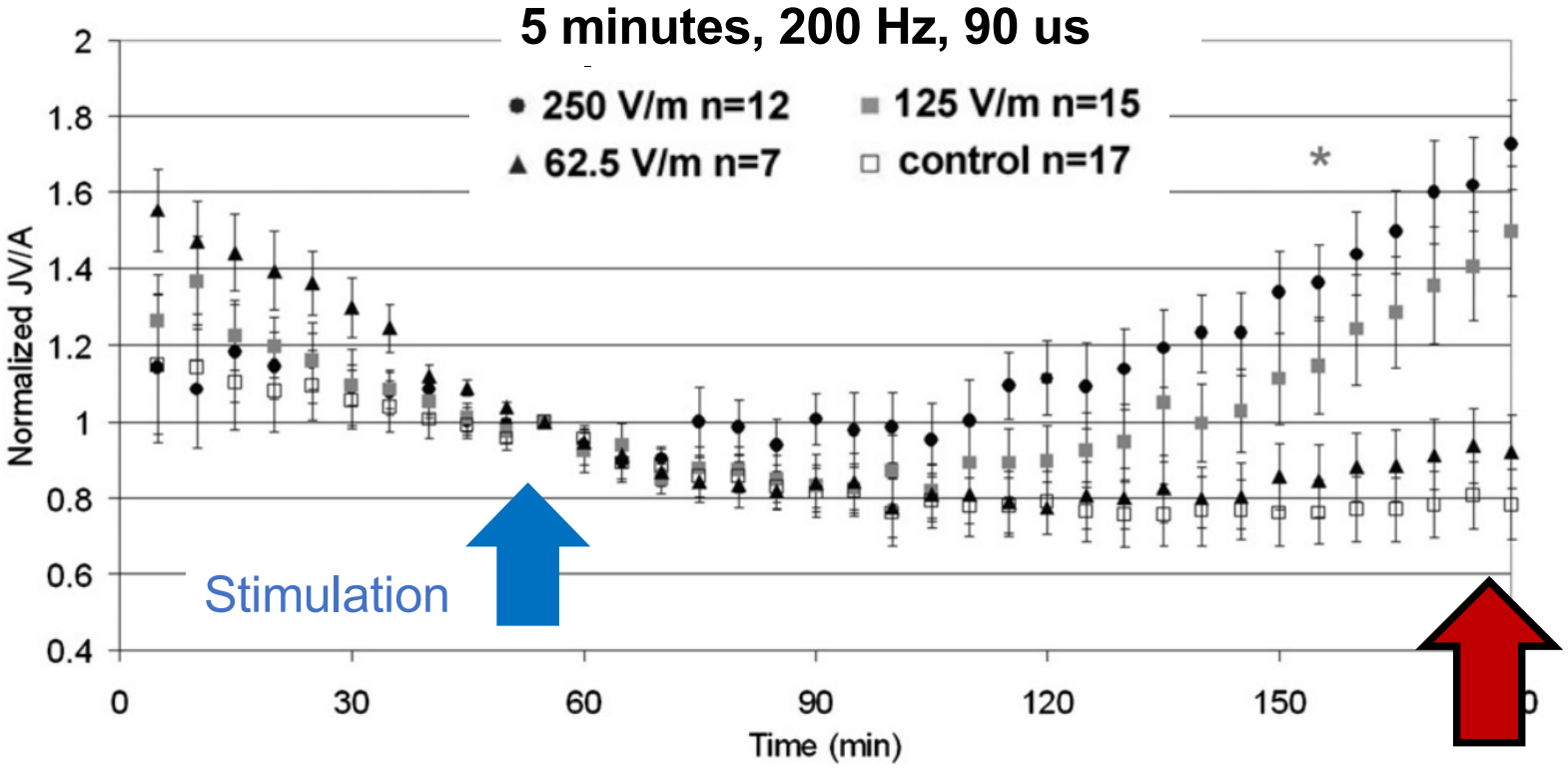
Xia et al. Direct Current Stimulation Disrupts Endothelial Glycocalyx and Tight Junctions of the Blood-Brain Barrier in vitro. *Frontiers cell and developmental biology* 2021

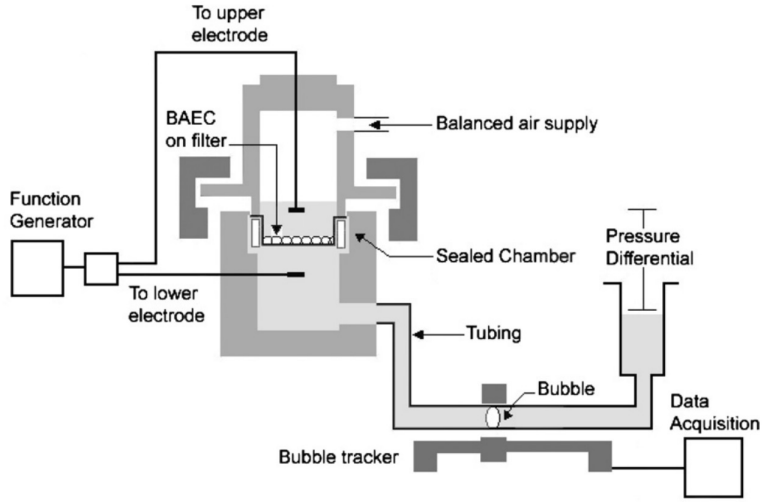
Plasticity from brain vasculature stimulation.

Cancel et al. Direct current stimulation of endothelial monolayers induces…transport. *Scientific Reports* 2019

Cancel et al. Direct current stimulation modulates gene expression in isolated astrocytes with implications for glia-mediated plasticity. *Scientific Reports* 2022

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

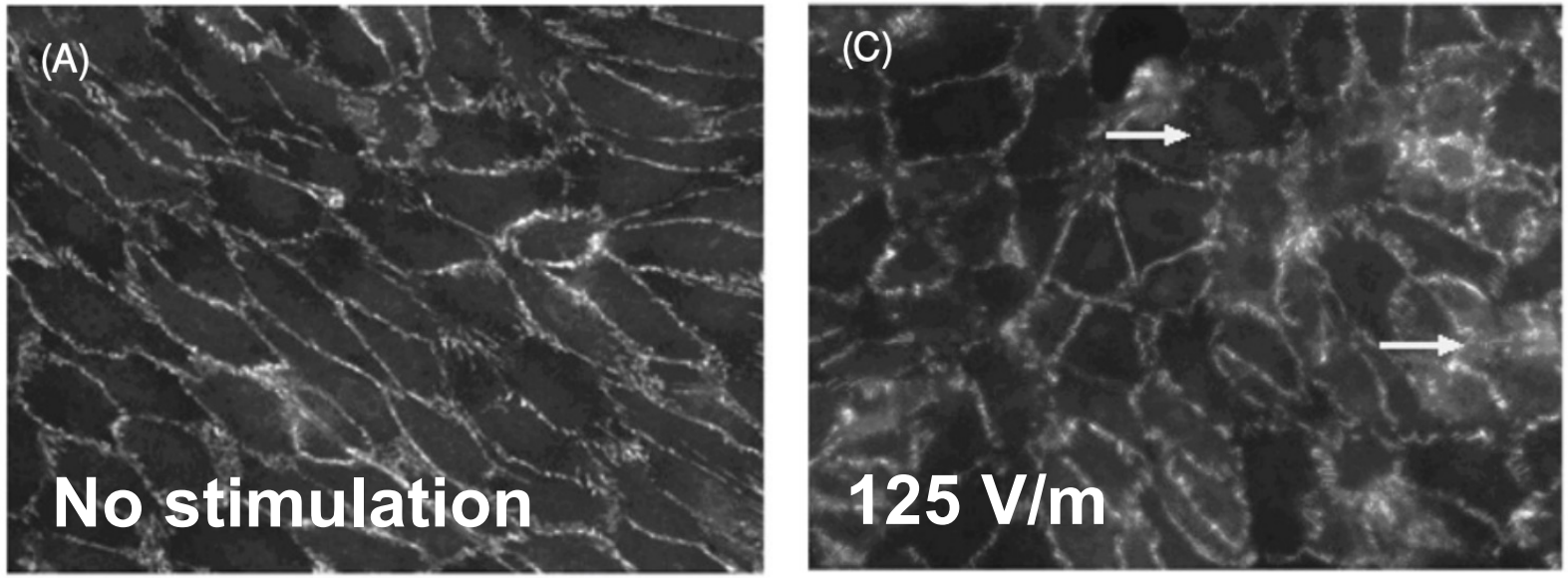




Increased water transport across BBB model following 5 min high-intensity pulsed electric field

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

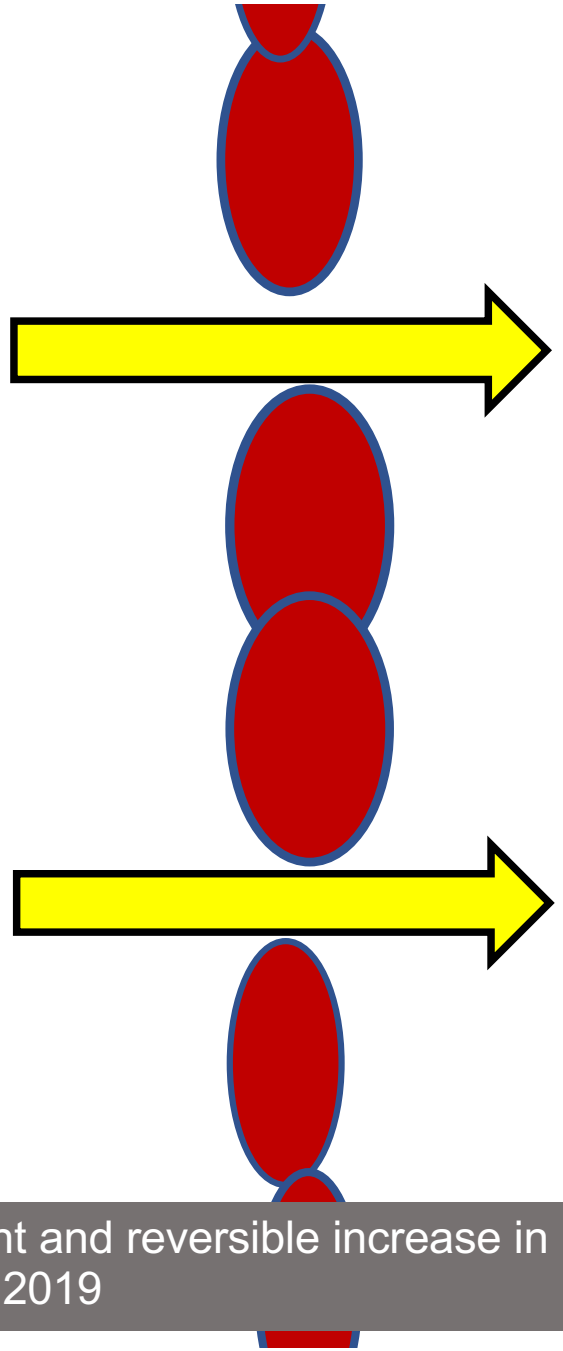
ZO-1 tight junction protein surrounds endothelial cells in control. Pulses electric fields modify continuity (arrows).

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

Static or Pulsed electric fields increase hydraulic conductivity of in vitro endothelial monolayers

- Increased water transport likely enhances solute transport (impacting neurons)
- Dose dependent (so controllable) increase in BBB transport
- **Via modulation / opening peri-cellular Tight Junctions**.

- No evidence for cell electroporation / transmembrane transport.
- Plausible in any brain / spinal structures / peripheral
- In vitro BBB system may not be good model for long-term (reversible) changes



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

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

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

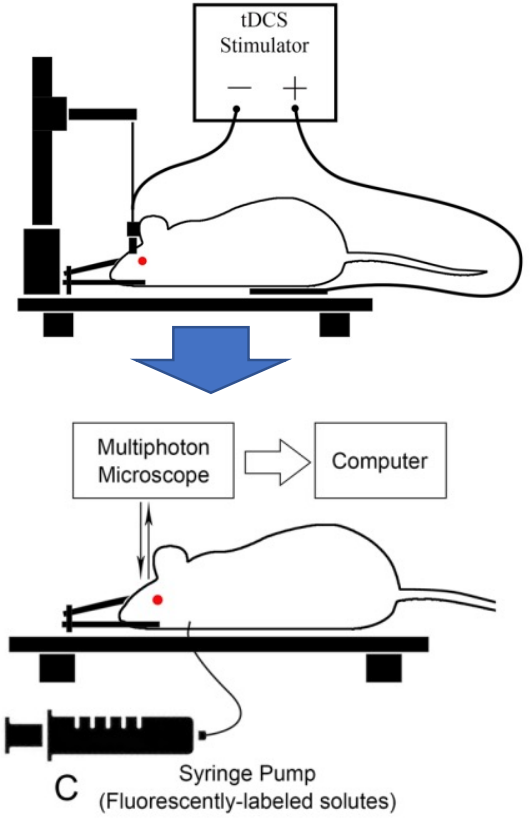
- Cancel et al. DCS of endothelial monolayers induces a transient and reversible increase in transport due to electroosmotic. *Sci Reports* 2019
- Shin et al. In Vivo Modulation of the Blood-Brain Barrier Permeability by tDCS. *Ann Biomed Eng*. 2020

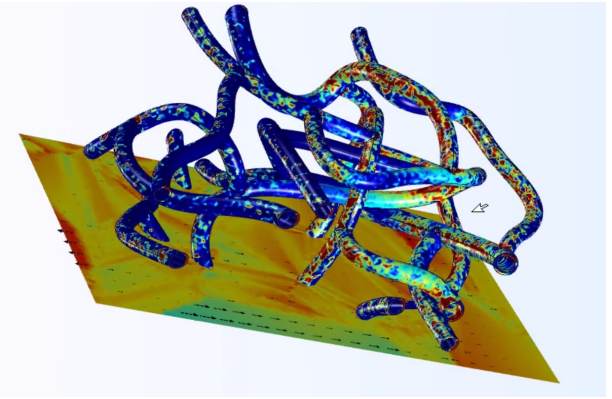
Drive brain clearance (eg. dementia)

- 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

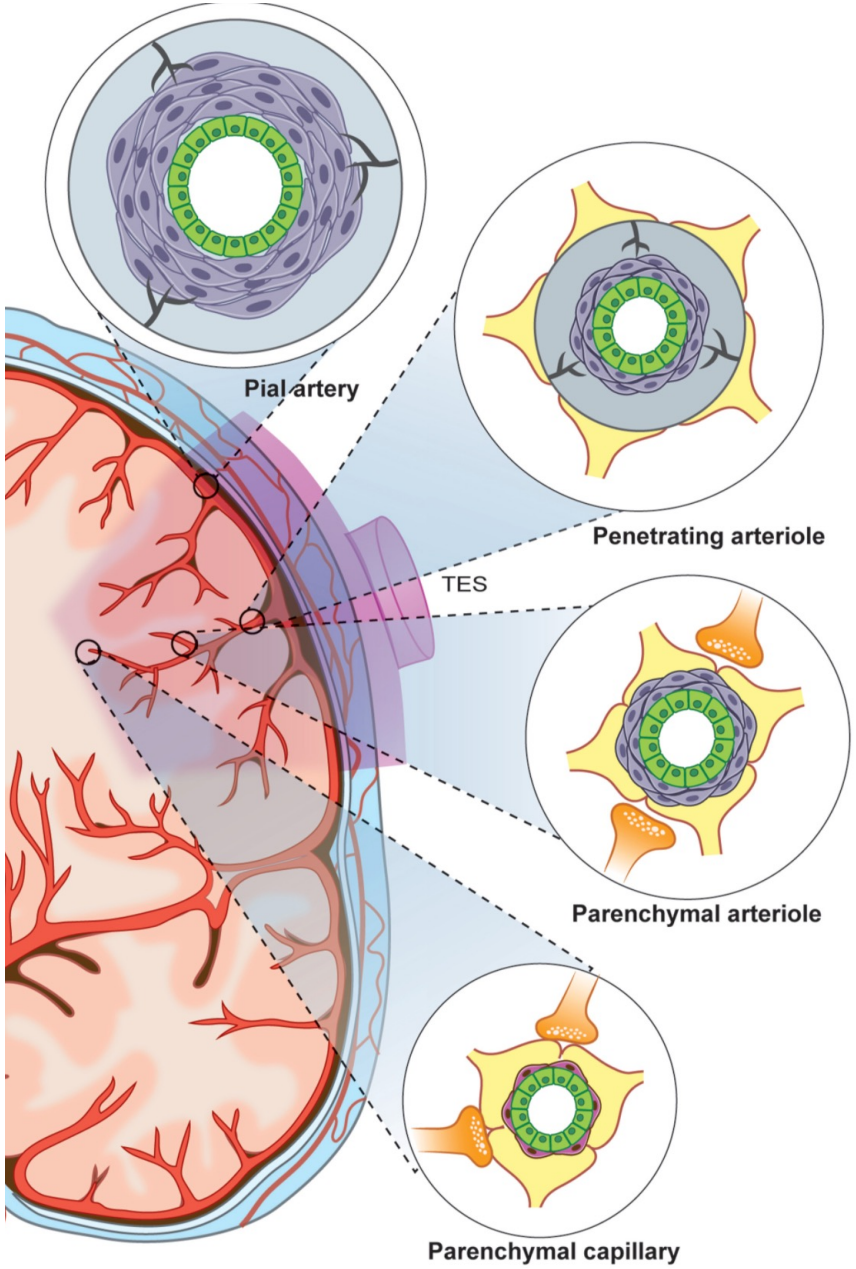
Neuro-protective role (acute stroke)

- Bahr Hosseini et al. Central Nervous System Electrical Stimulation for Neuroprotection in Acute Cerebral Ischemia: Meta-Analysis of Preclinical Studies. *Stoke* 2019

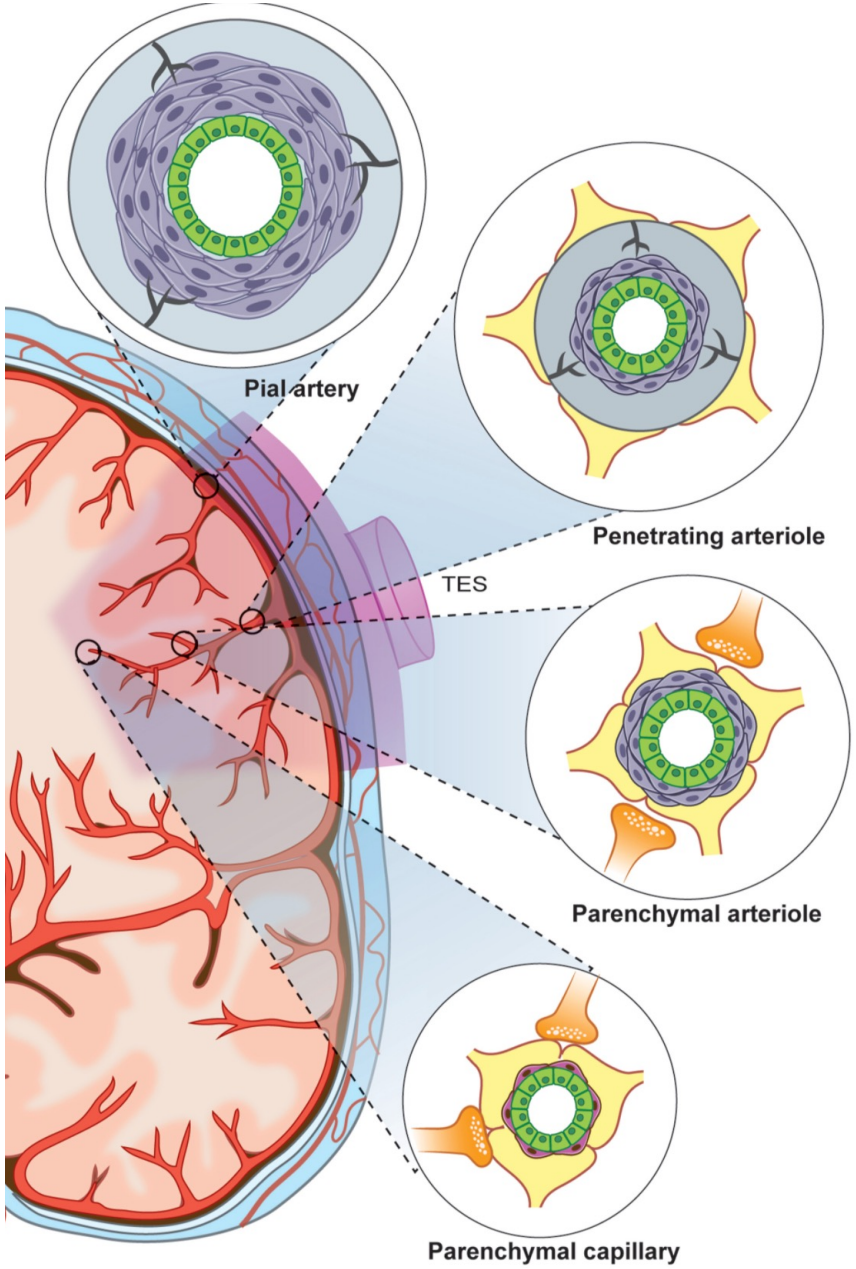




Why neurovascular modulation?



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.

Dural Surface/Arteries · Perivascular nerves · Perivascular Space · Smooth muscle cells
Endothelium · Astrocytic end feet · Neurons of neurovascular unit · Pericytes

FIRST ASPECT: Neuronal stimulation must consider neurovascular coupling.

SECOND ASPECT: Direct stimulation of brain vasculature.

Perivascular neurons-mediated pathway	Endothelial-mediated pathway
Astrocytic-mediated pathway	Neurovascular unit neurons-mediated pathway

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

Neurocapillary-modulation

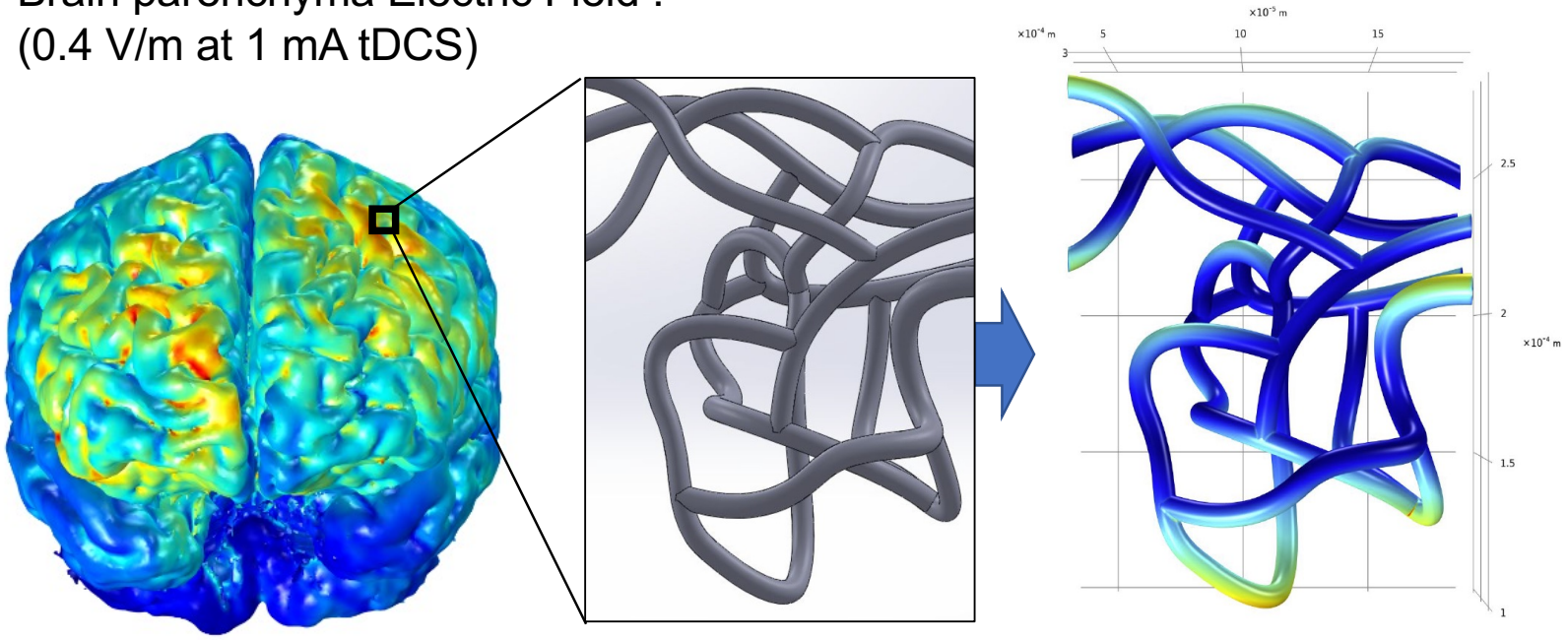
Second aspect: Direct stimulation of brain vascular/ blood-brain-barrier function.

Endothelial-mediated pathway

Neurovascular modulation

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

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



Multi-scale models with brain vasculature structure.

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).

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

Neurocapillary-modulation

Third aspect: Fundamentally changing how neurons are directly stimulated

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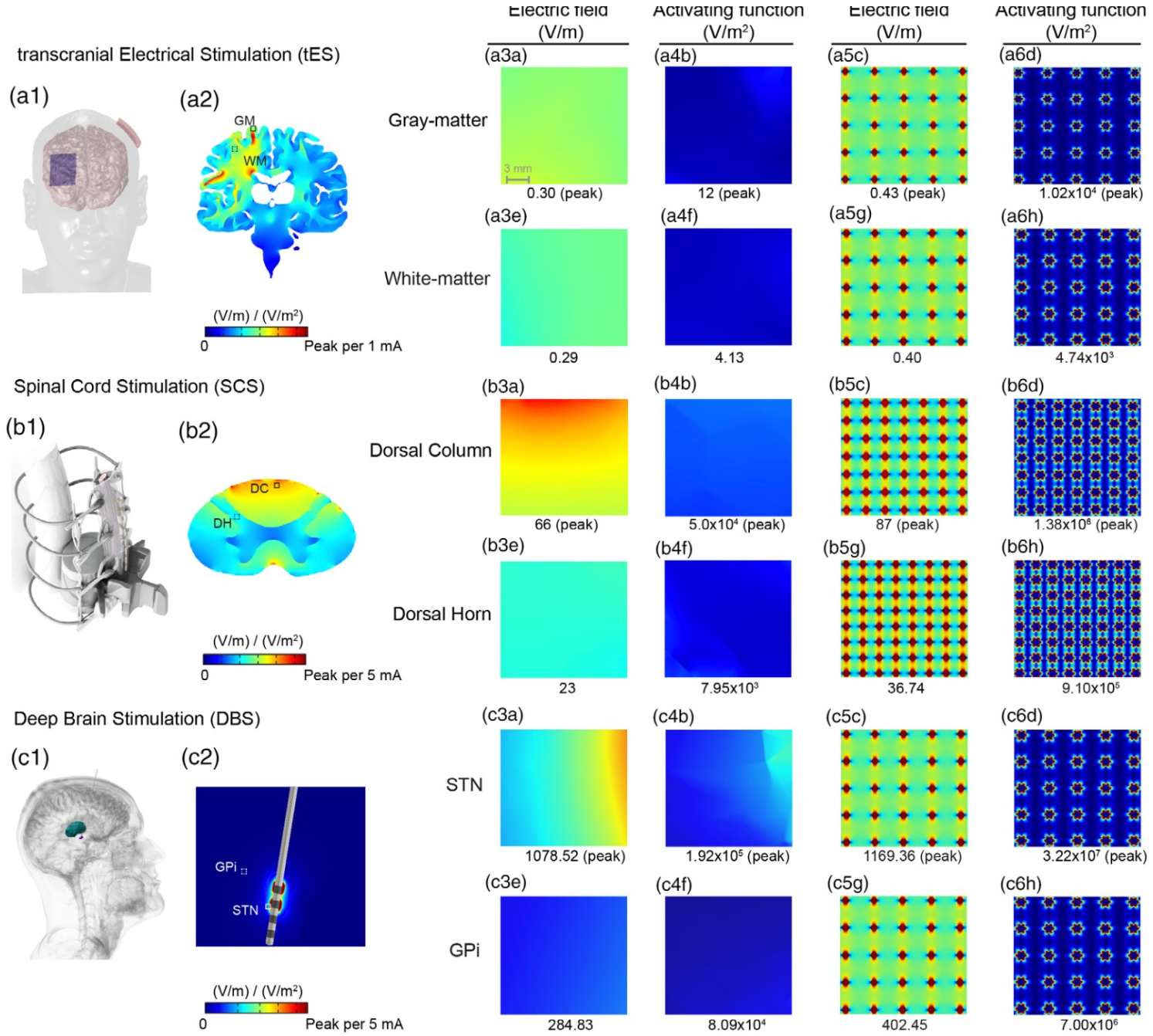


Application of neurocapillary-modulation in tES, DBS, and SCS. Degree and spatial extent of electrical current flow distortion in the brain parenchyma around brain capillaries and the resulting amplification of neuronal polarization, driving factors such as electric field and activating function

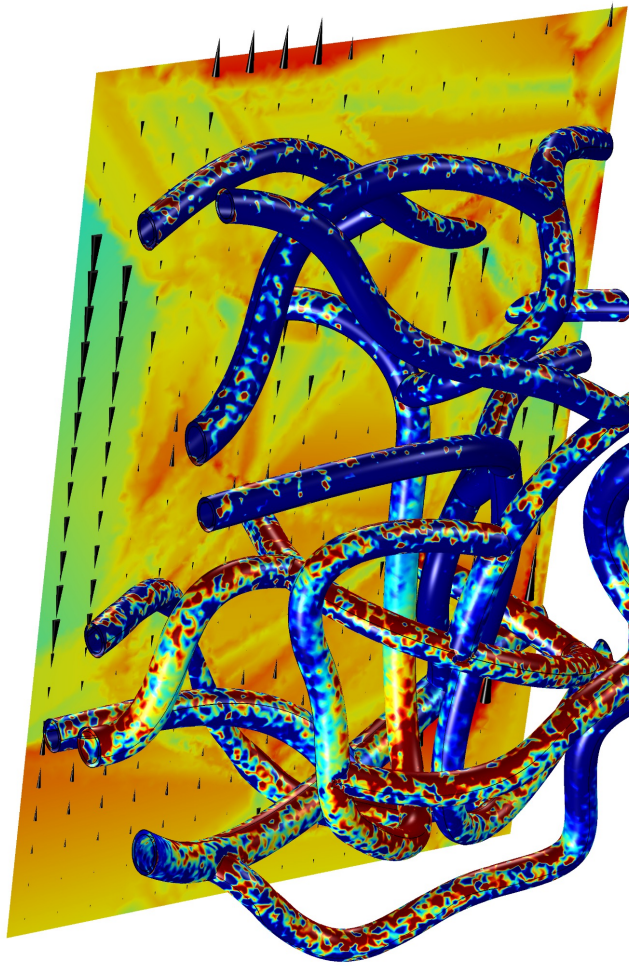
Khadka et al. Neurocapillary-modulation. Neuromodulation: Technology at the Neural Interface. 2020

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.
These dependencies can predict system / behavioral scale outcomes. And suggests unique therapy strategies (brain "flushing..:.)

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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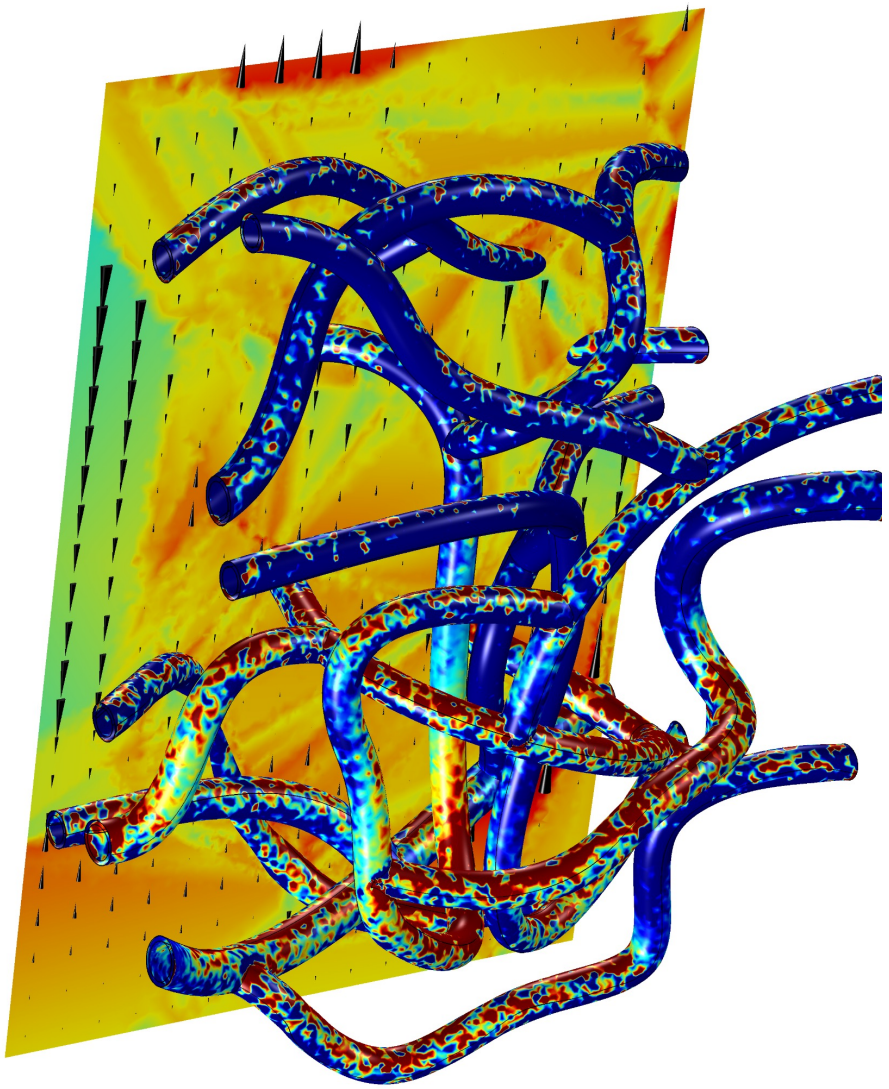

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