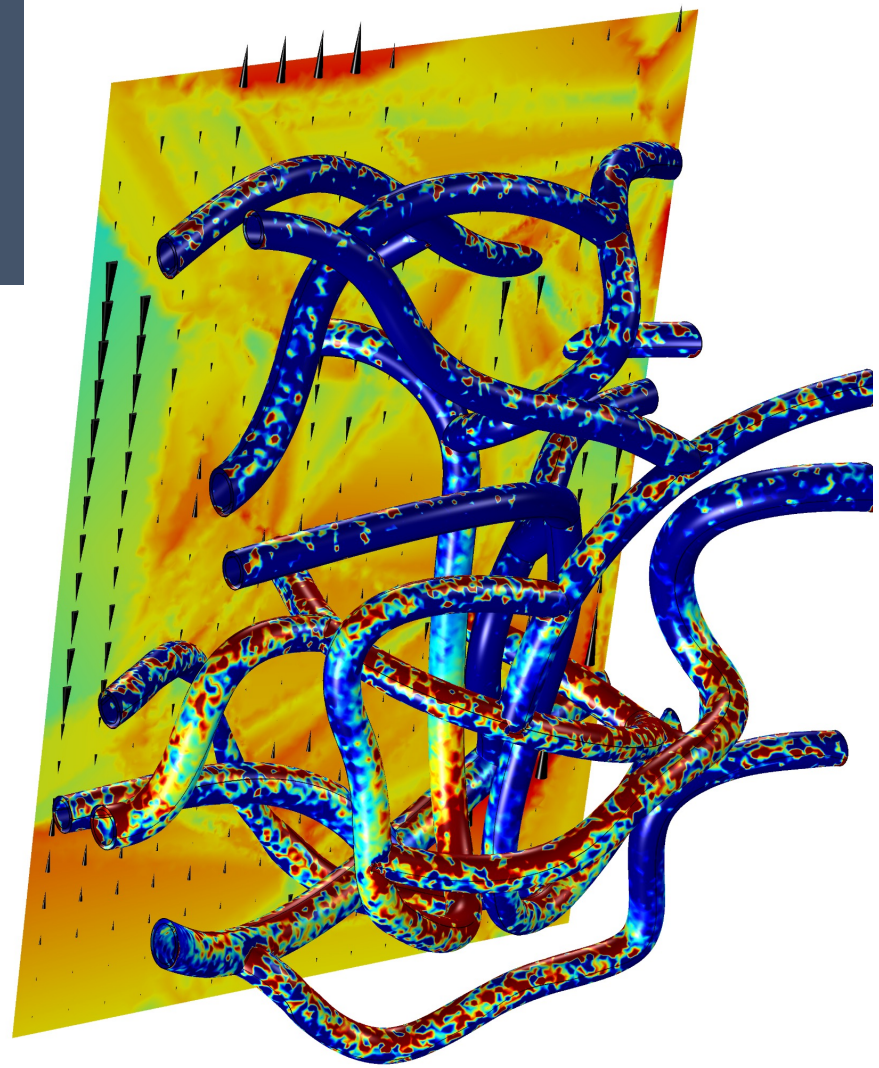
Functional Neuroimaging as the Key to Effective Neurostimulation: Neuro-vascular Modulation?

Marom Bikson
The City College of New York

Lucas Parra, Jacek Dmochowski, John Tarbell, Bingmei Fu, Greg Kronberg, Abhishek Datta, Niranjan Khadka, Adantchede L. Zannou, Zeinab Esmaeilpour, Nigel Gebodh, Gozde Unal, Mohamad FallahRad, Brian Kopell, Yifan Xia, Limary Cancel, Scott Lempka, Sandra V Lopez-Quintero, Andy Huang, Dennis Truong, Tianhe Zhang, Brad Hershey, Rosana Esteller



NEBEC 2023. Drexel University, Philadelphia

Disclosure

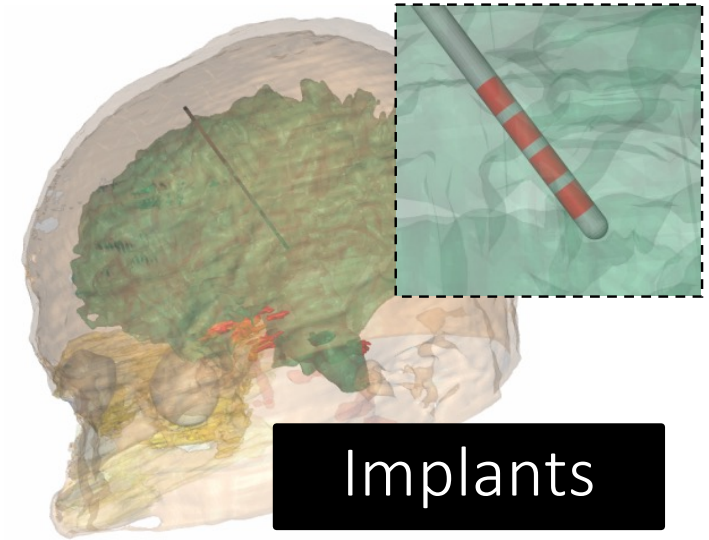
The City University of New York: Patents on brain stimulation.
Soterix Medical: Produces tDCS and High-Definition tDCS.
Grants, assigned inventions, and/or serves SAB for SafeToddles, Boston Scientific, GlaxoSmithKline, Biovisics, Mecta, Lumenis, Halo Neuroscience, Google-X, i-Lumen, Remz, Humm, Allergan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

Slides @MaromBikson

Support

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

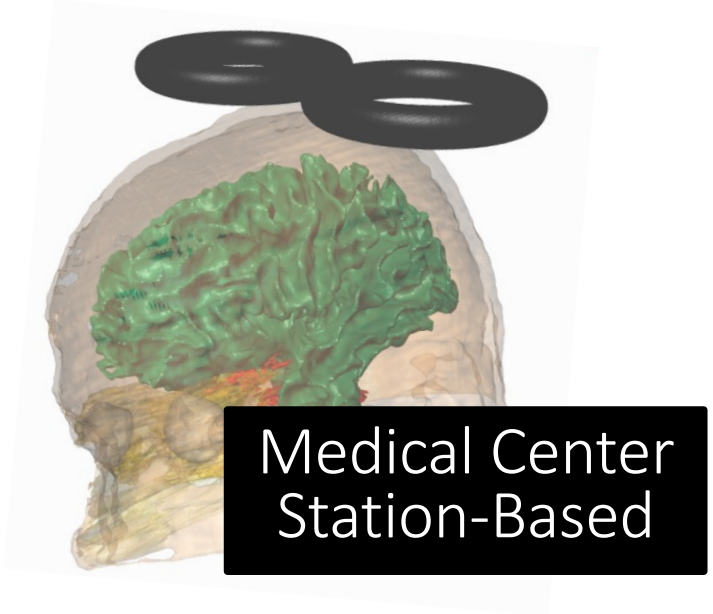
Neuromodulation technologies platforms vary in how energy is delivered to what target.



Deep Brain Stimulation (DBS)

Spinal Cord Stimulation (SCS)

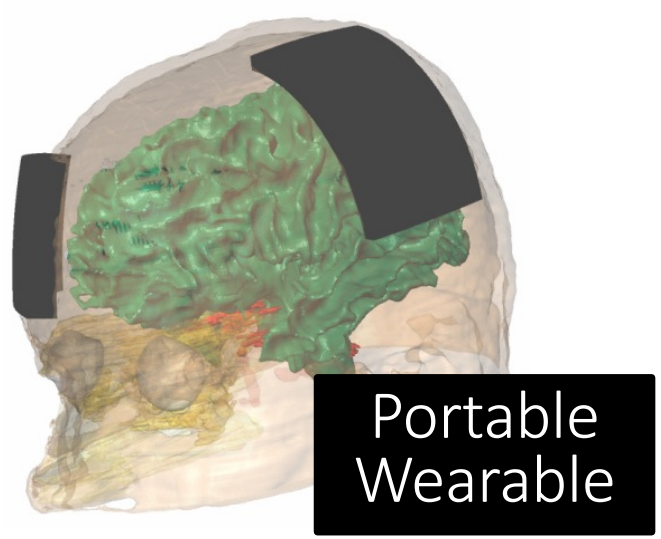
Peripheral Nerve Stimulation



Transcranial Magnetic Stimulation (TMS)

Electroconvulsive Therapy

High-Definition tES (HD-tES)

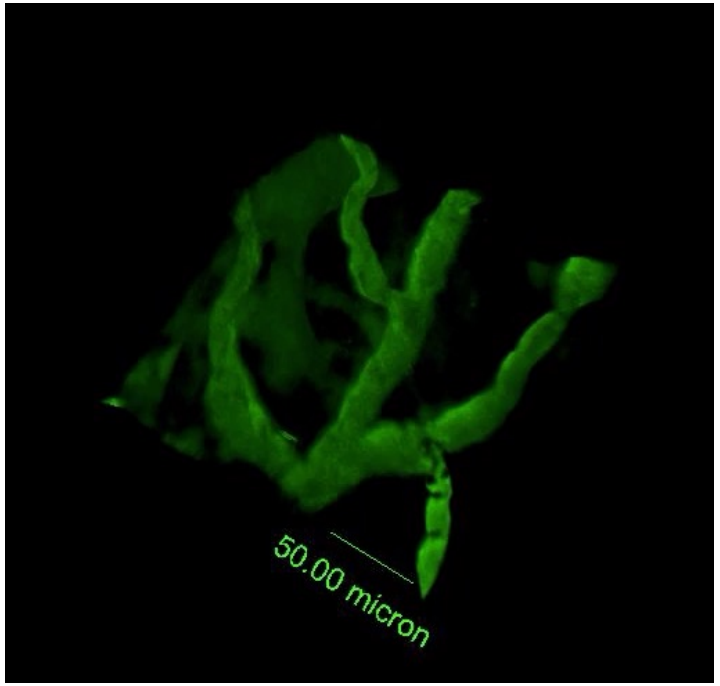


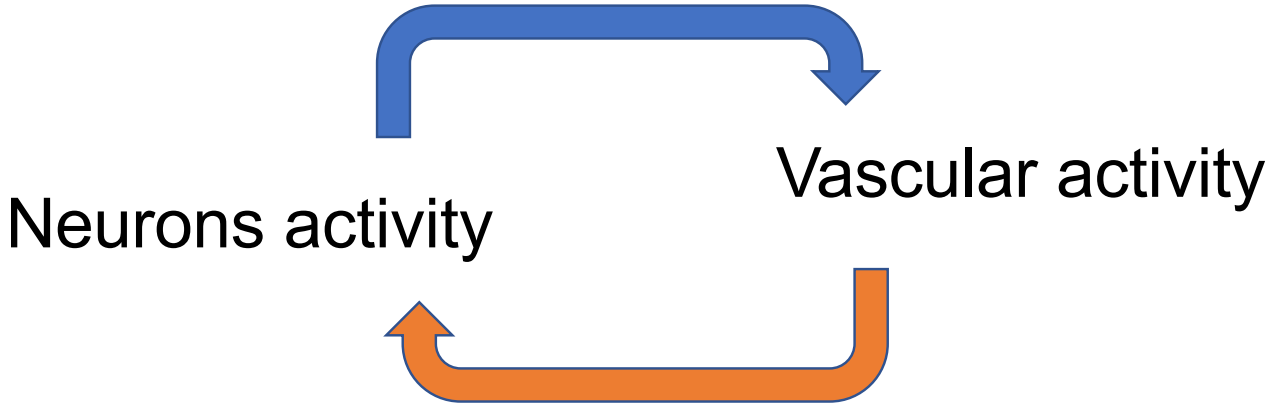
Transcranial Electrical Stimulation (tES) / tDCS

Non-invasive vagus nerve simulation / taVNS

Neuromodulation effects on brain function can be measured using hemodynamic-based imaging.

- **Neurovascular coupling (unit):** Coupling between neuronal activity, vascular flow and blood-brain barrier (BBB) permeability, and glia.
- **Two-way interaction**. Neuronal activity activates vascular system. Vascular system modulates brain function.





frontiers in Systems Neuroscience

TECHNOLOGY REPORT
published: 09 March 2015
doi: 10.3389/fnsys.2015.00027

Wearable functional near infrared spectroscopy (fNIRS) and transcranial direct current stimulation (tDCS): expanding vistas for neurocognitive augmentation

*Ryan McKendrick[1], Raja Parasuraman[1] and Hasan Ayaz[2]**

[1] Center of Excellence in Neuroergonomics, Technology, and Cognition (CENTEC), George Mason University, Fairfax, VA, USA, [2] School of Biomedical Engineering, Science and Health Systems, Drexel University, Philadelphia, PA, USA

- What brain regions are activated by stimulation and how (boosted or inhibited, for how long)?
- Does underlying brain state (a task) impact effects of stimulation?
- What stimulation dose is best?

Credit: Soterix Medical

Neuromodulation technique

Nervous System

Neuronal stimulation

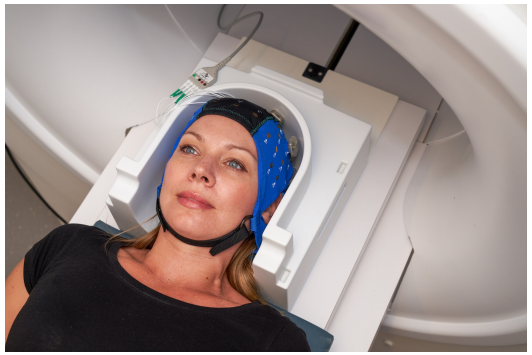
Hemodynamic-response based on neuro-vascular coupling

Hemodynamic-based imaging

Infer response of nervous system (neurons).

The hemodynamic signal is **an epiphenomena** of the neuronal-response to neuromodulation.

Credit: Soterix Medical



I propose that studies using hemodynamic based imaging (fNIRS, fMRI…) of brain stimulation are not recognizing full value of data collected.

Neuromodulation technique

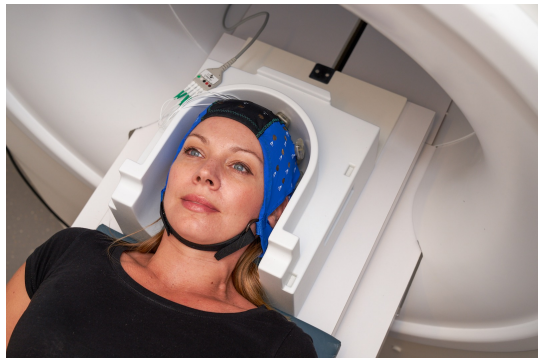
Nervous System

Direct vascular stimulation

Neuronal response secondary to brain vascular changes.

Hemodynamic-based imaging

Credit: Soterix Medical

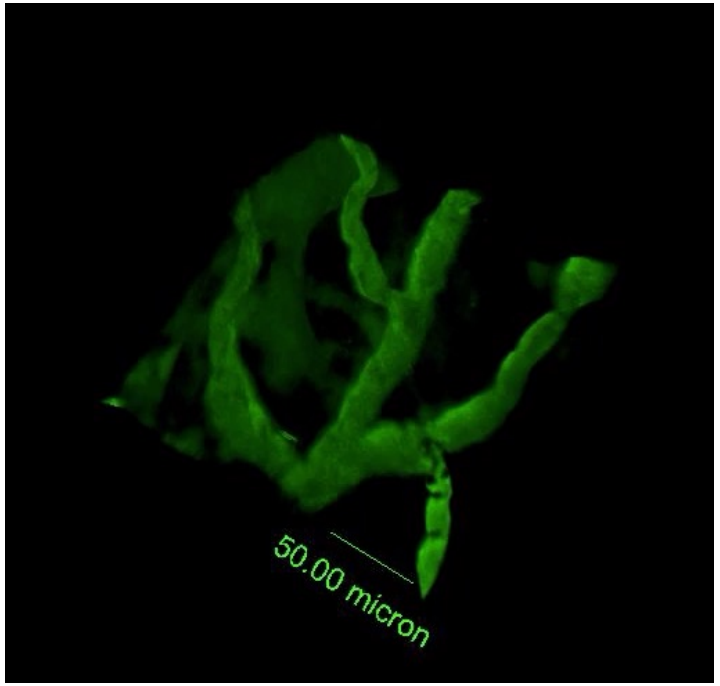


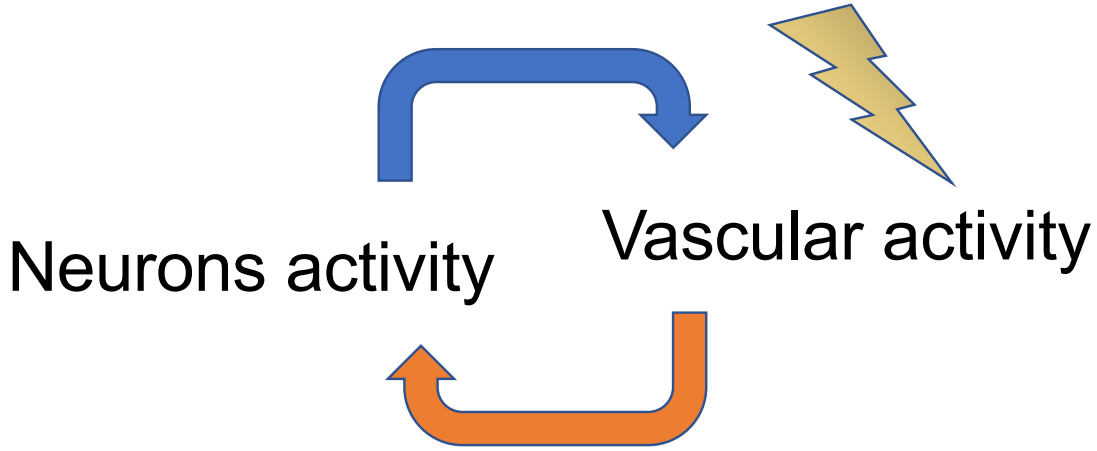
Measure vascular response of nervous system to stimulation.

The hemodynamic signal is **not** an epiphenomena of the neuronal-response to neuromodulation.

Infer how vascular stimulation then modulates neuronal function.

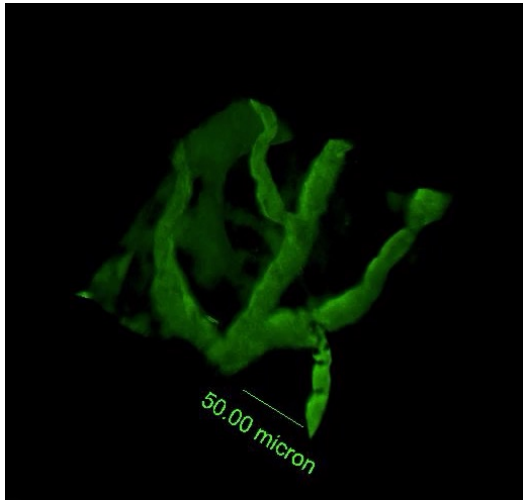
- **Neurovascular coupling (unit):** Coupling between neuronal activity, vascular flow and blood-brain barrier (BBB) permeability, and glia.
- **Two-way interaction**. Neuronal activity activates vascular (eg. fMRI), Transport across BBB tightly controlled to regulate brain function.



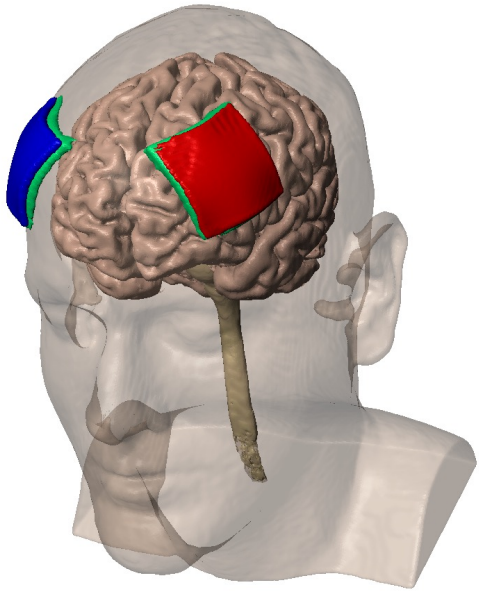


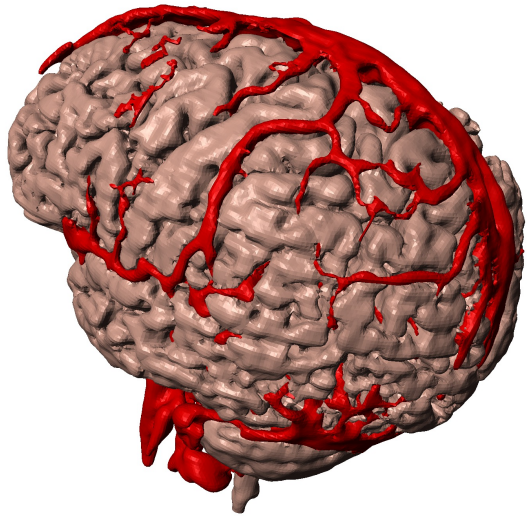
Can neuromodulation **directly** activate endothelial cells of the BBB, leading to secondary neuronal changes.

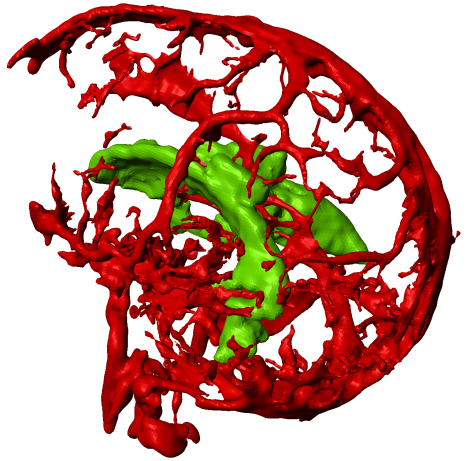
Transcranial Direct Current Stimulation (tDCS) of the BBB



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







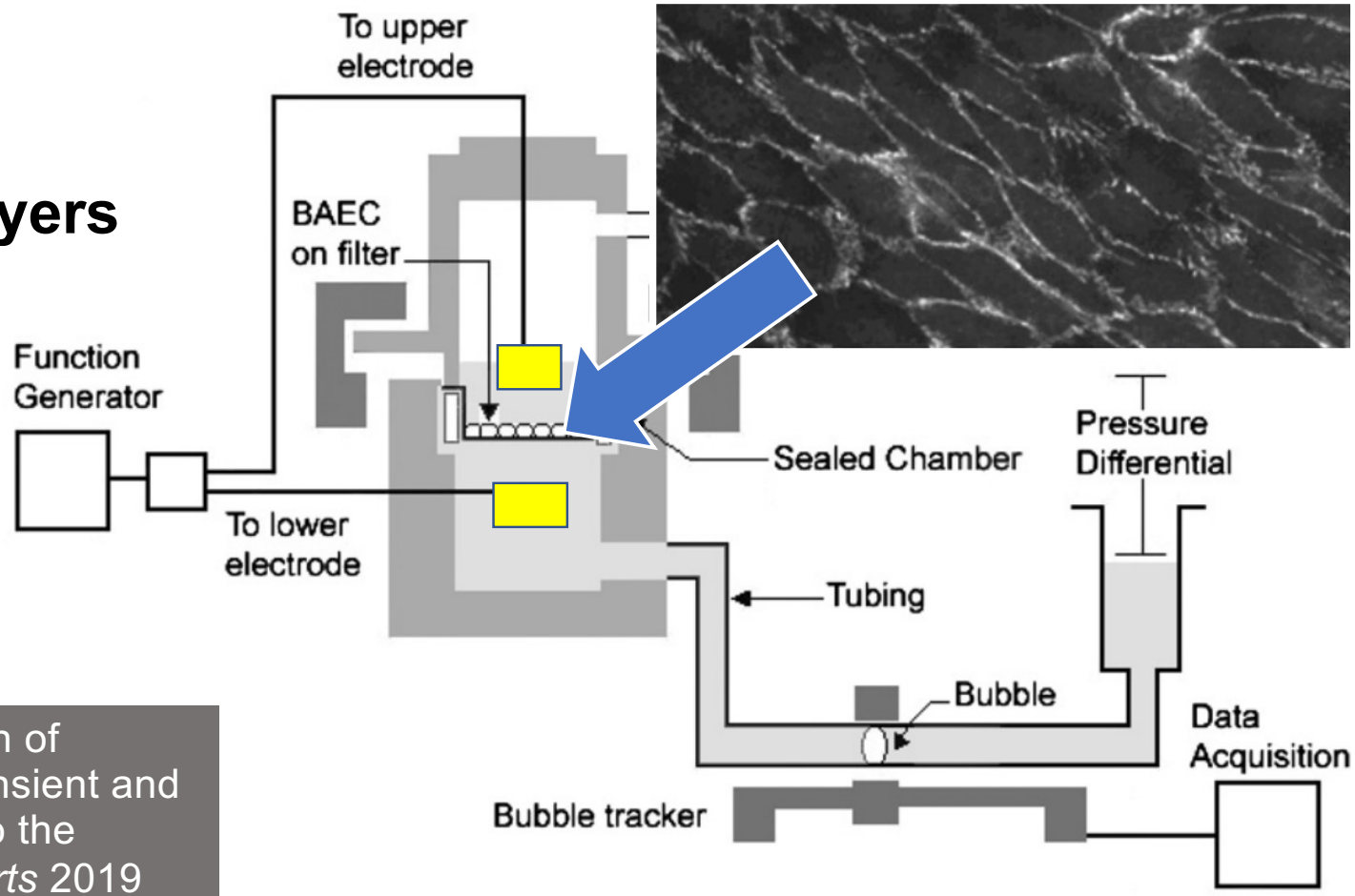
Can tDCS (DC fields) directly activate the BBB, which in turn modulates neurons?

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.

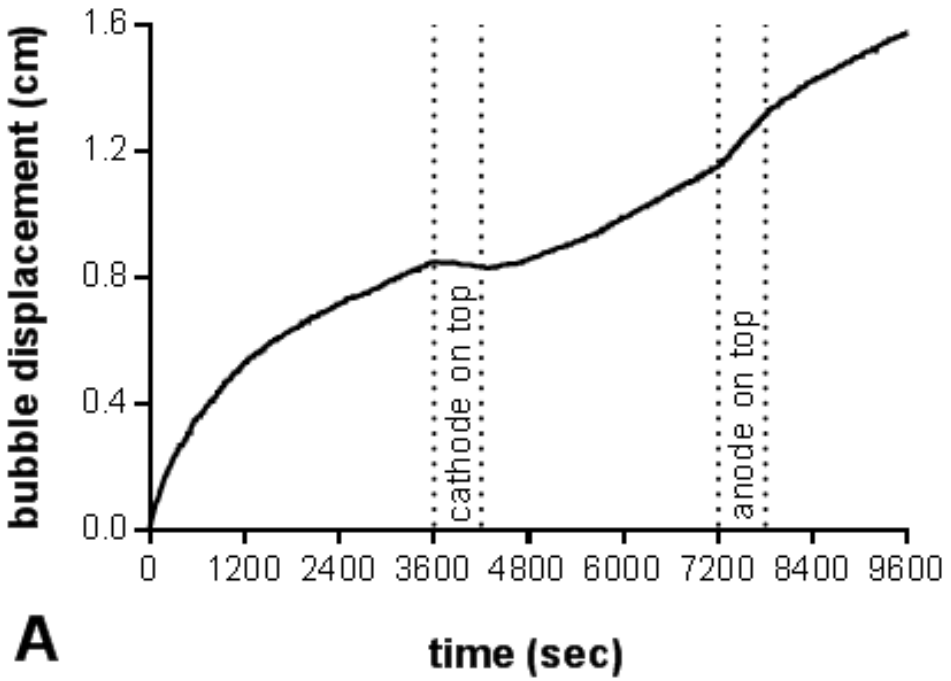
Isolated BBB stimulation established direct neuromodulation.

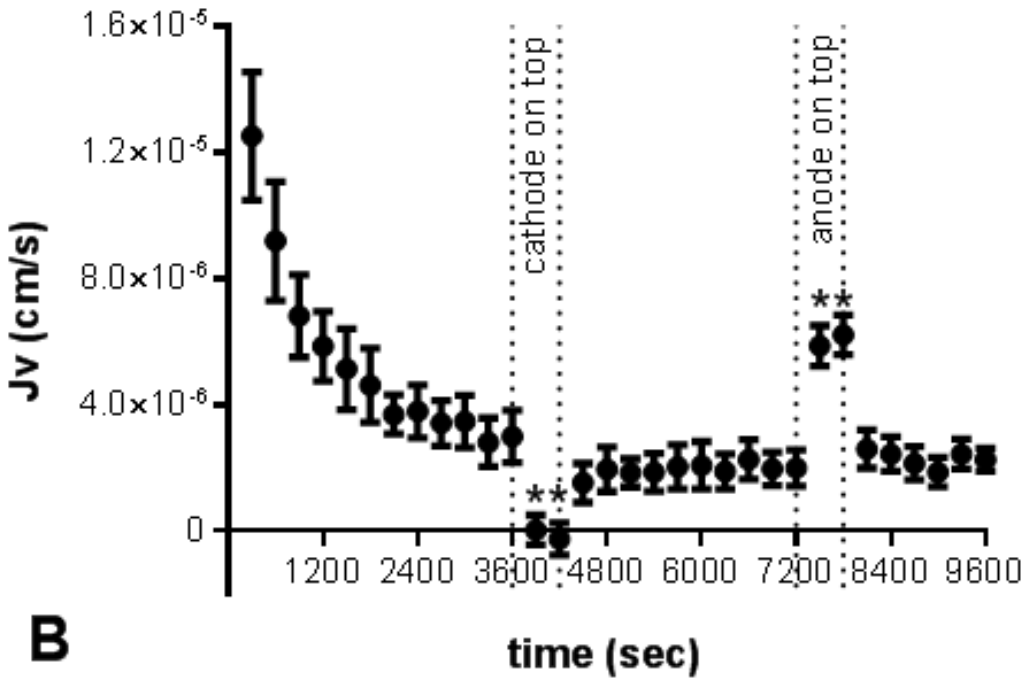
BBB model: **cultured endothelium monolayers**



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

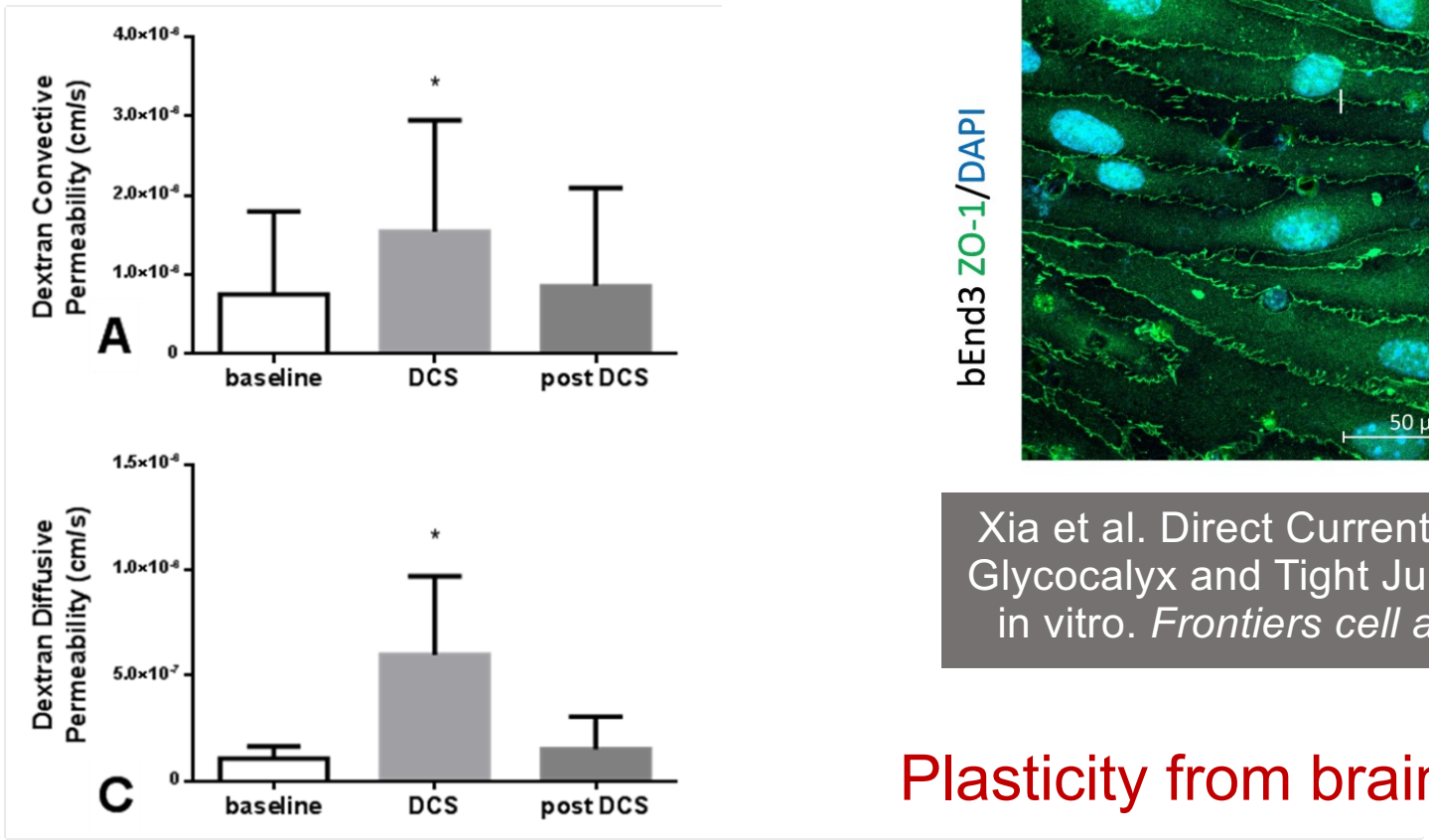


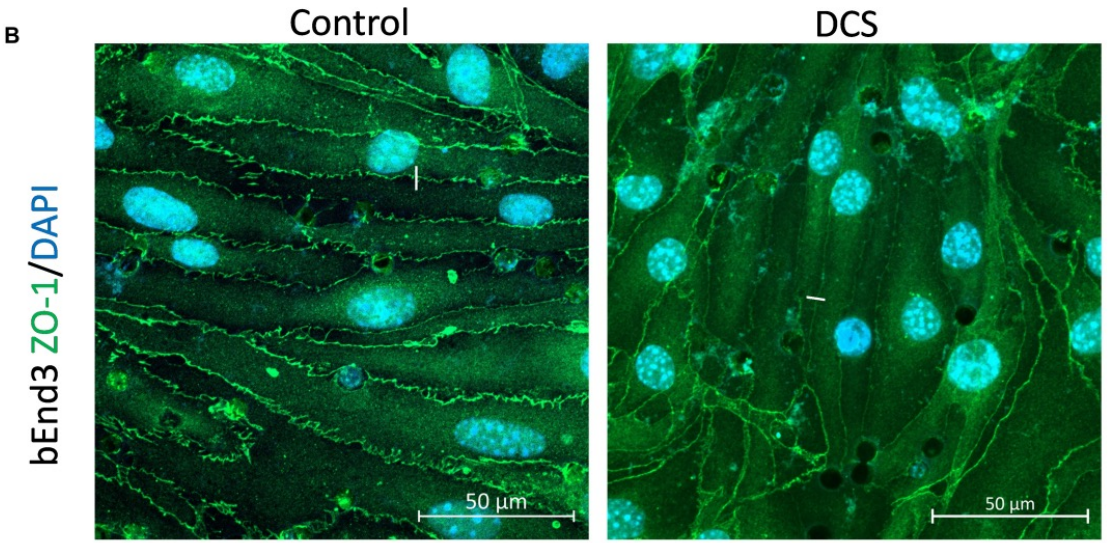


Electroosmosis: Current will drag water through a (charged) barrier, proportional to tightness of barrier.

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).



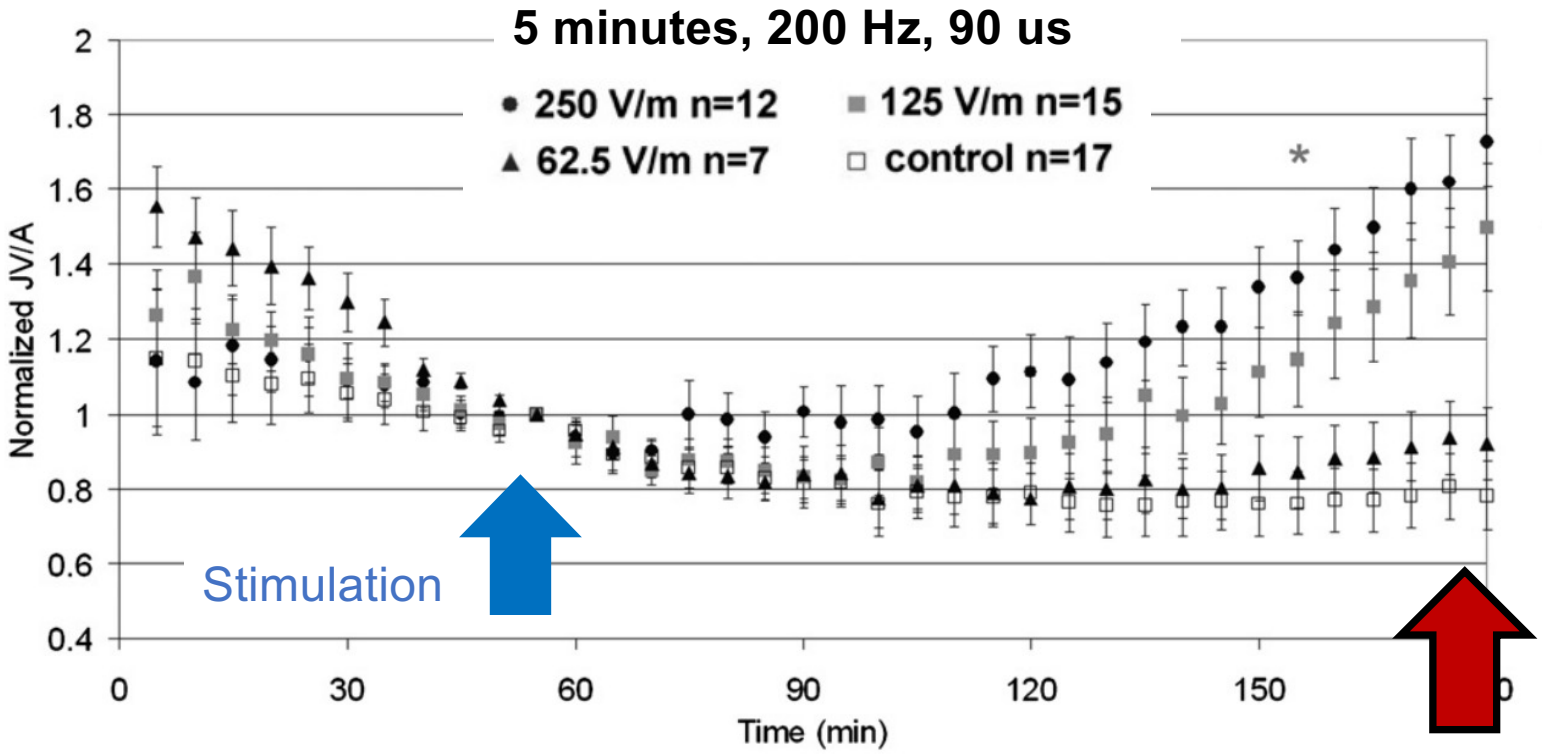


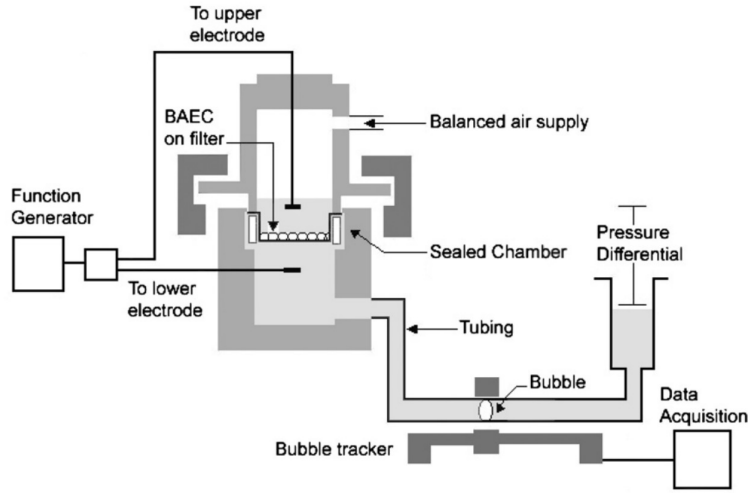
Xia et al. Direct Current Stimulation Disrupts Endothelial Glycocalyx and Tight Junctions of the Blood-Brain Barrier in vitro. *Frontiers cell and developmental biology* 2021

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 modulate isolated endothelial cells (BBB) including water and transport flux.

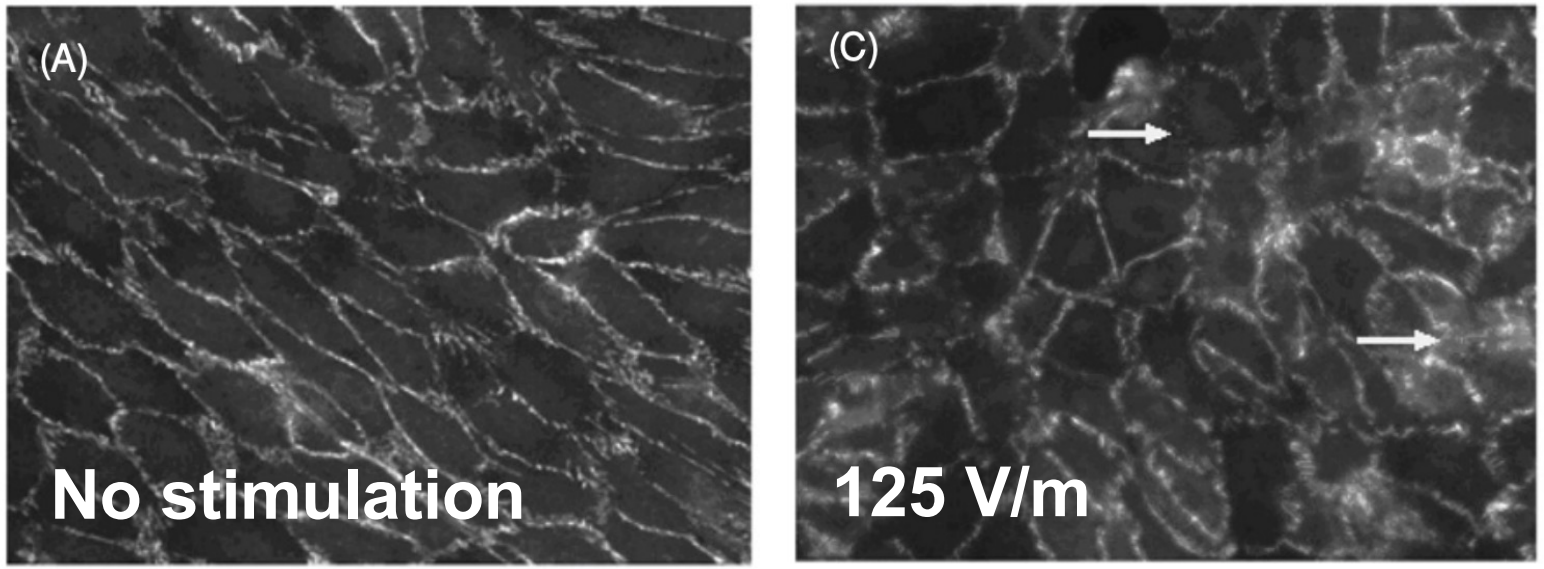




Increased water transport across BBB model following 5 min high-intensity pulsed electric field

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

Lasting (plastic) changes in endothelial cells (BBB) function.

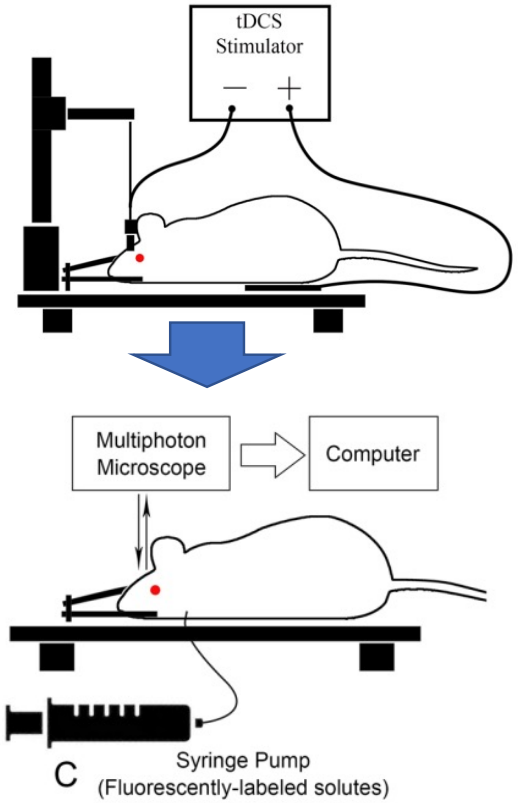


ZO-1 tight-junction protein staining

ZO-1 tight junction protein surrounds endothelial cells in control. Pulsed 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)

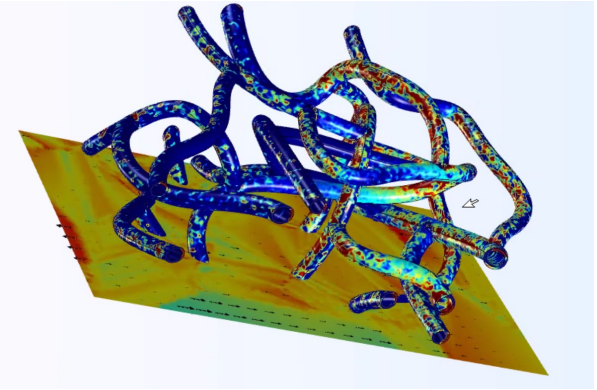


”Boosting” of brain function (transport) / neurorehabilitation efficacy

- 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

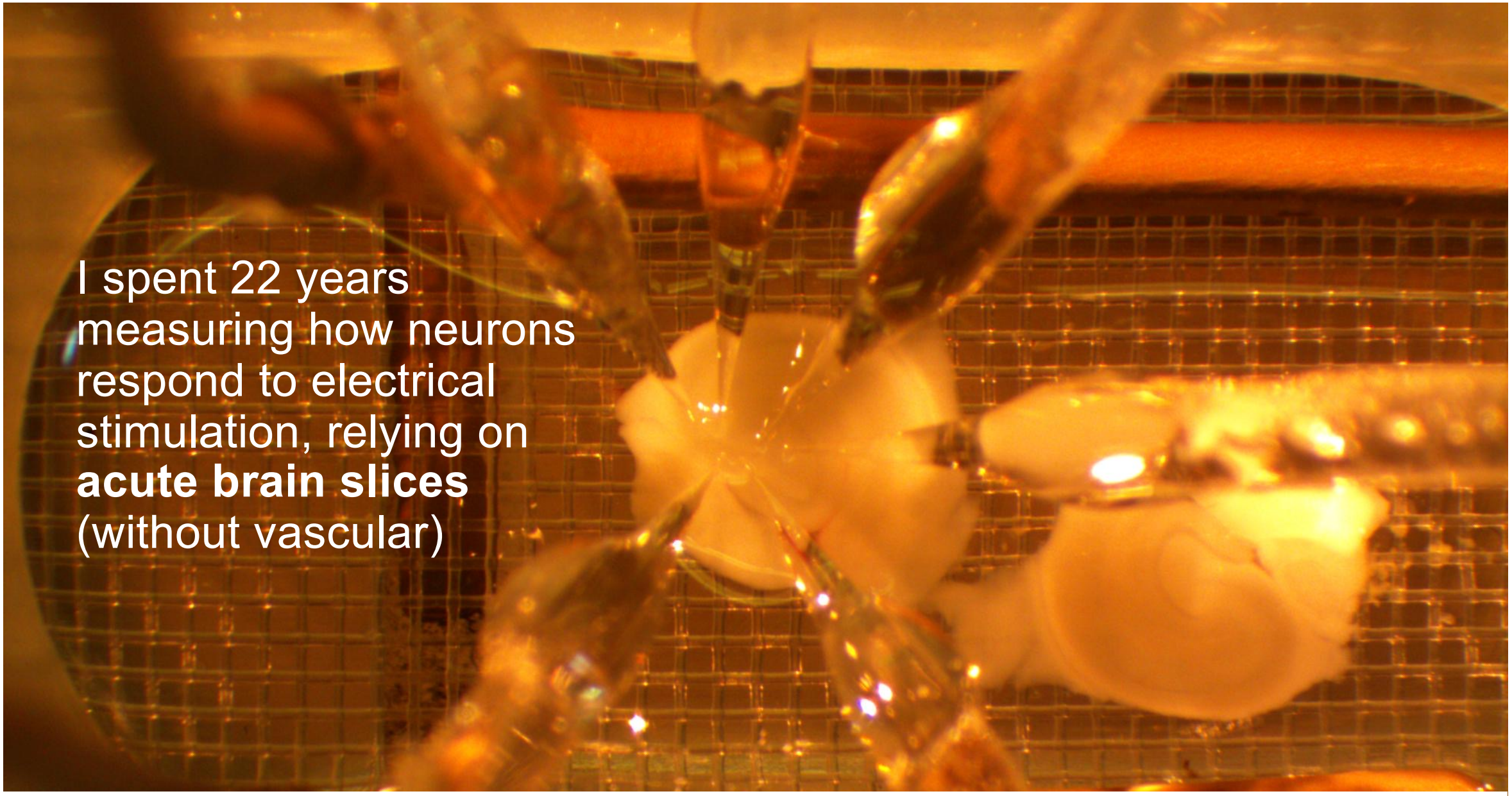
Drive brain clearance (eg. dementia)

- 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



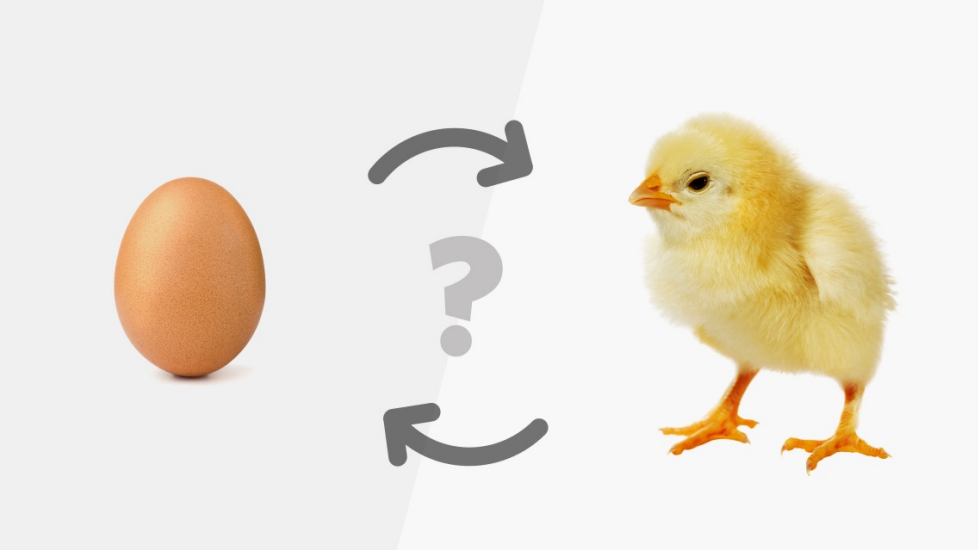
Neuro-protective role (acute stroke)

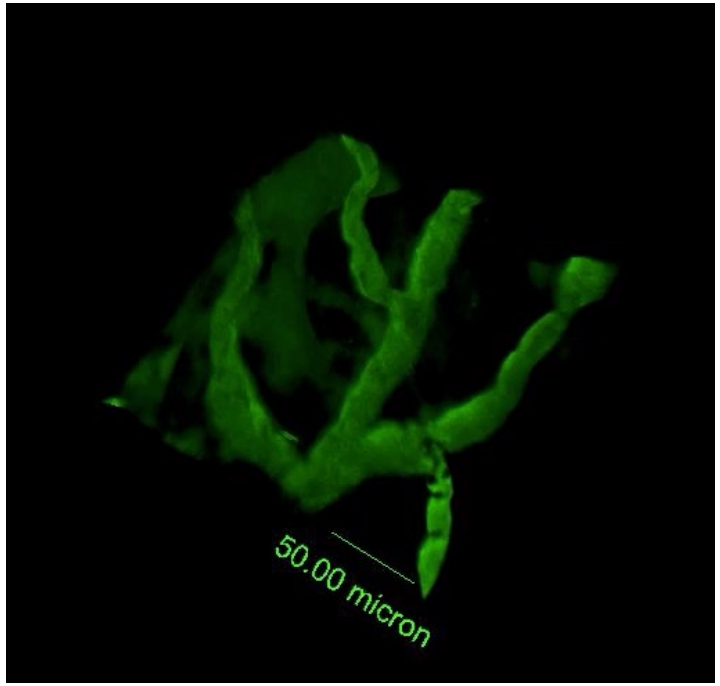
- Bahr Hosseini et al. CNS Electrical Stimulation for Neuroprotection in Acute Cerebral Ischemia: Meta-Analysis of Preclinical Studies. *Stoke* 2019

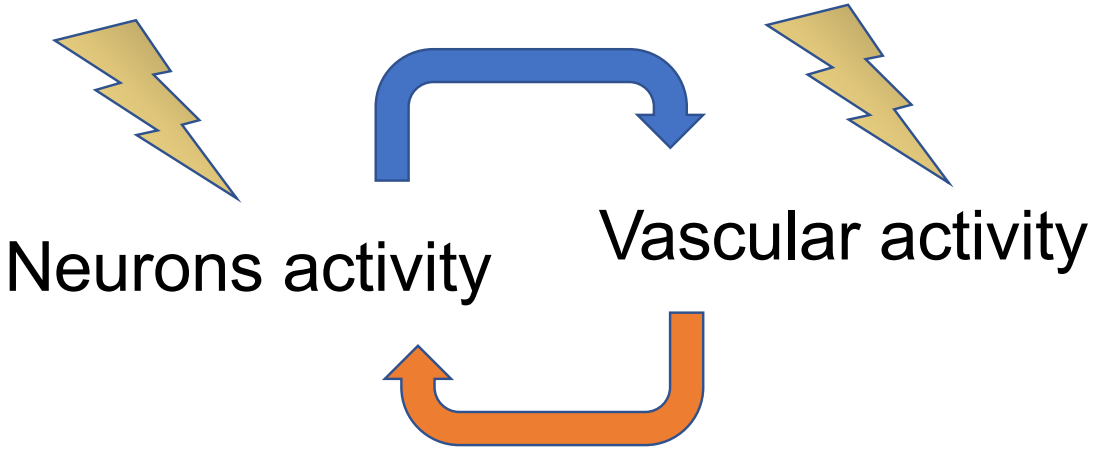


Jackson et al. Animal models of transcranial direct current stimulation. *Clin Neurophys* 2016

A problem.







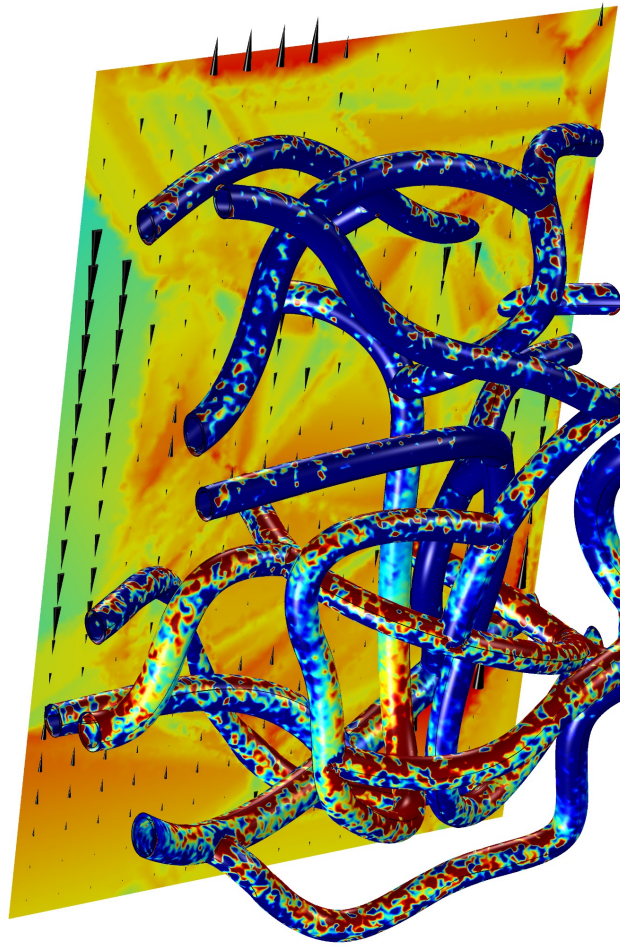
In so far as **neurovascular coupling** underpins brain function / disease / modulation, then **neuro** vs **vascular** effects are difficult to distinguish.

Three Aspects of Neuro-vascular Modulation

FIRST ASPECT: Stimulation 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
(glia activation, brain "flushing..:.)

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

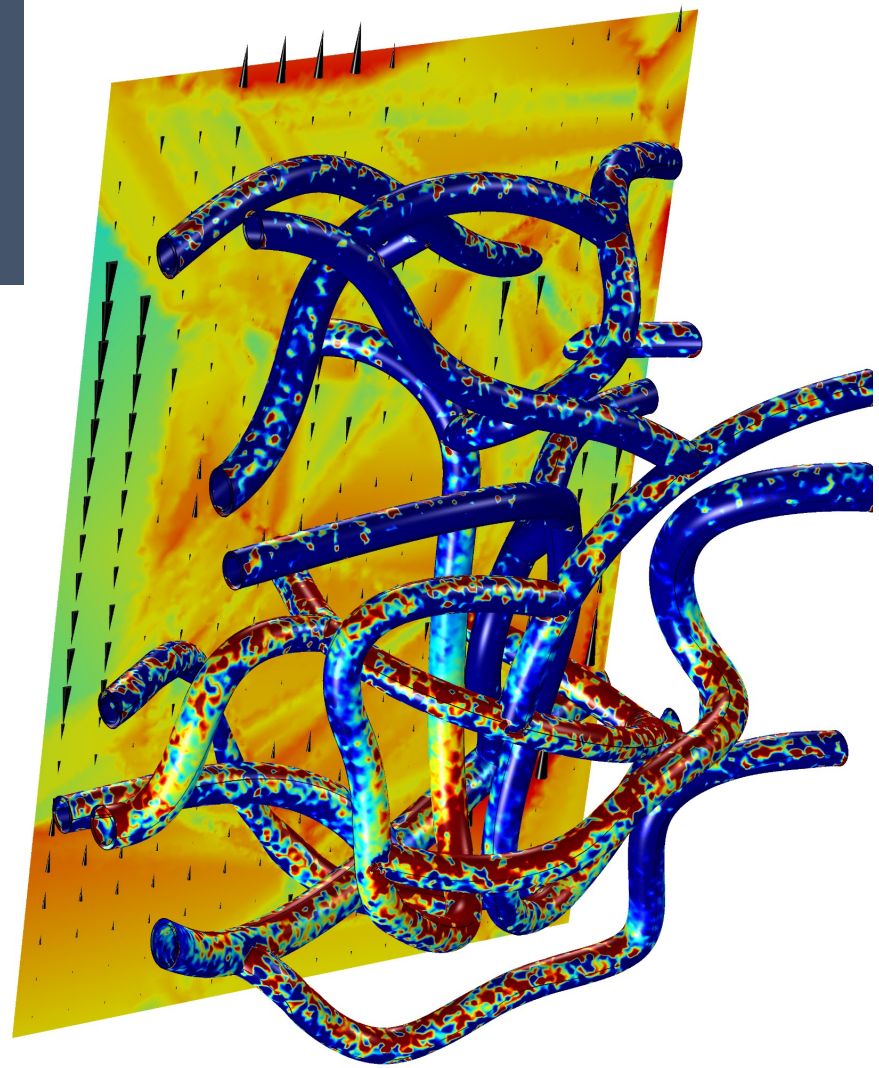


Multi-scale multi-physics model predict fluid "push" around brain during stimulation.

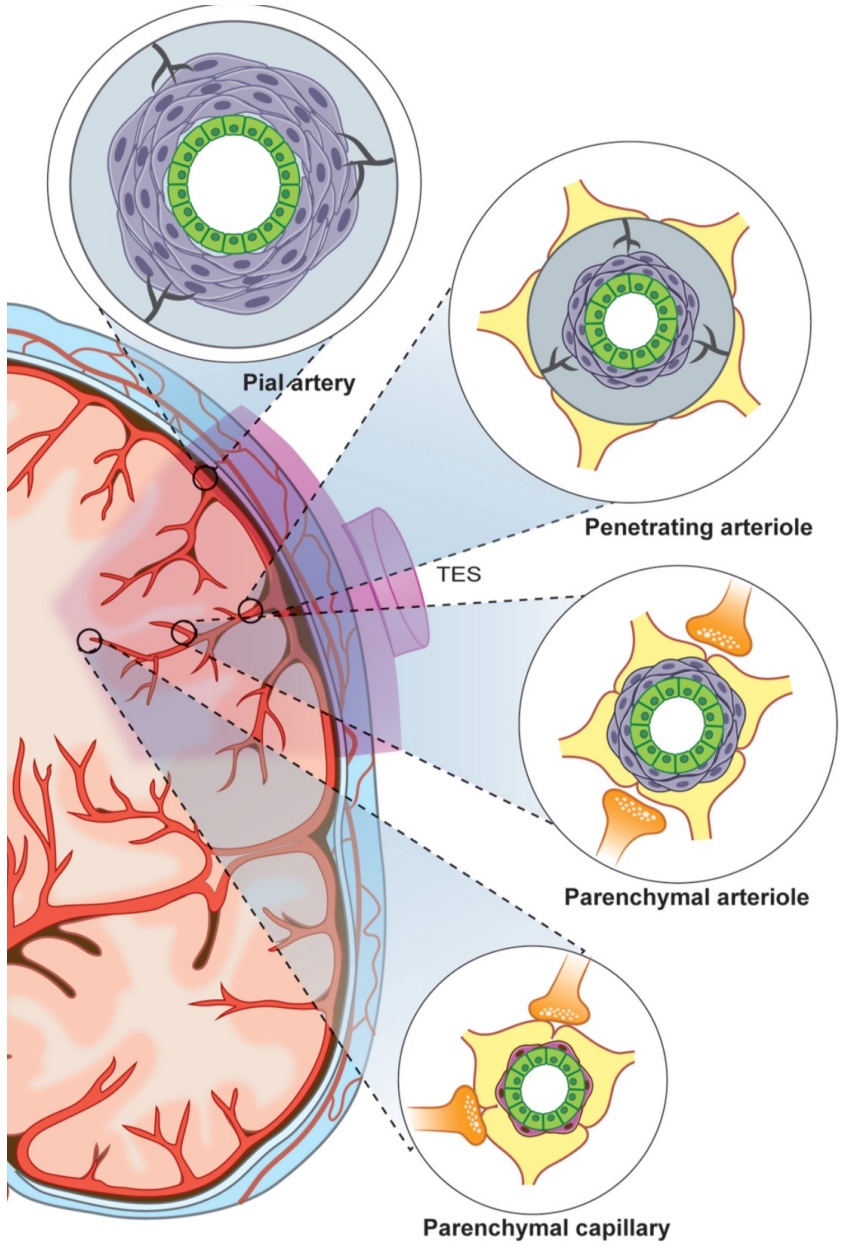
Functional Neuroimaging as the Key to Effective Neurostimulation: Neuro-vascular Modulation?

Marom Bikson
The City College of New York

Lucas Parra, Jacek Dmochowski, John Tarbell, Bingmei Fu, Greg Kronberg, Abhishek Datta, Niranjan Khadka, Adantchede L. Zannou, Zeinab Esmaeilpour, Nigel Gebodh, Gozde Unal, Mohamad FallahRad, Brian Kopell, Yifan Xia, Limary Cancel, Scott Lempka, Sandra V Lopez-Quintero, Andy Huang, Dennis Truong, Tianhe Zhang, Brad Hershey, Rosana Esteller



NEBEC 2023. Drexel University, Philadelphia



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

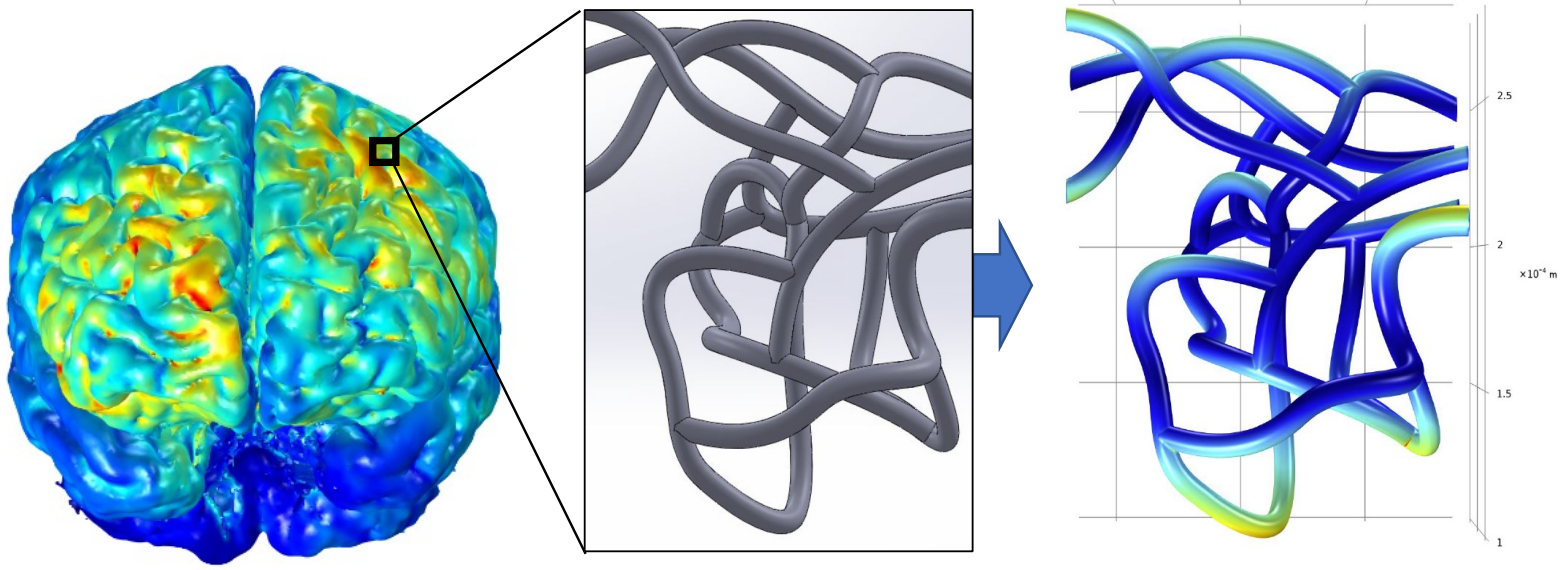
Second aspect: Direct stimulation of brain vascular/ blood-brain-barrier function.

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

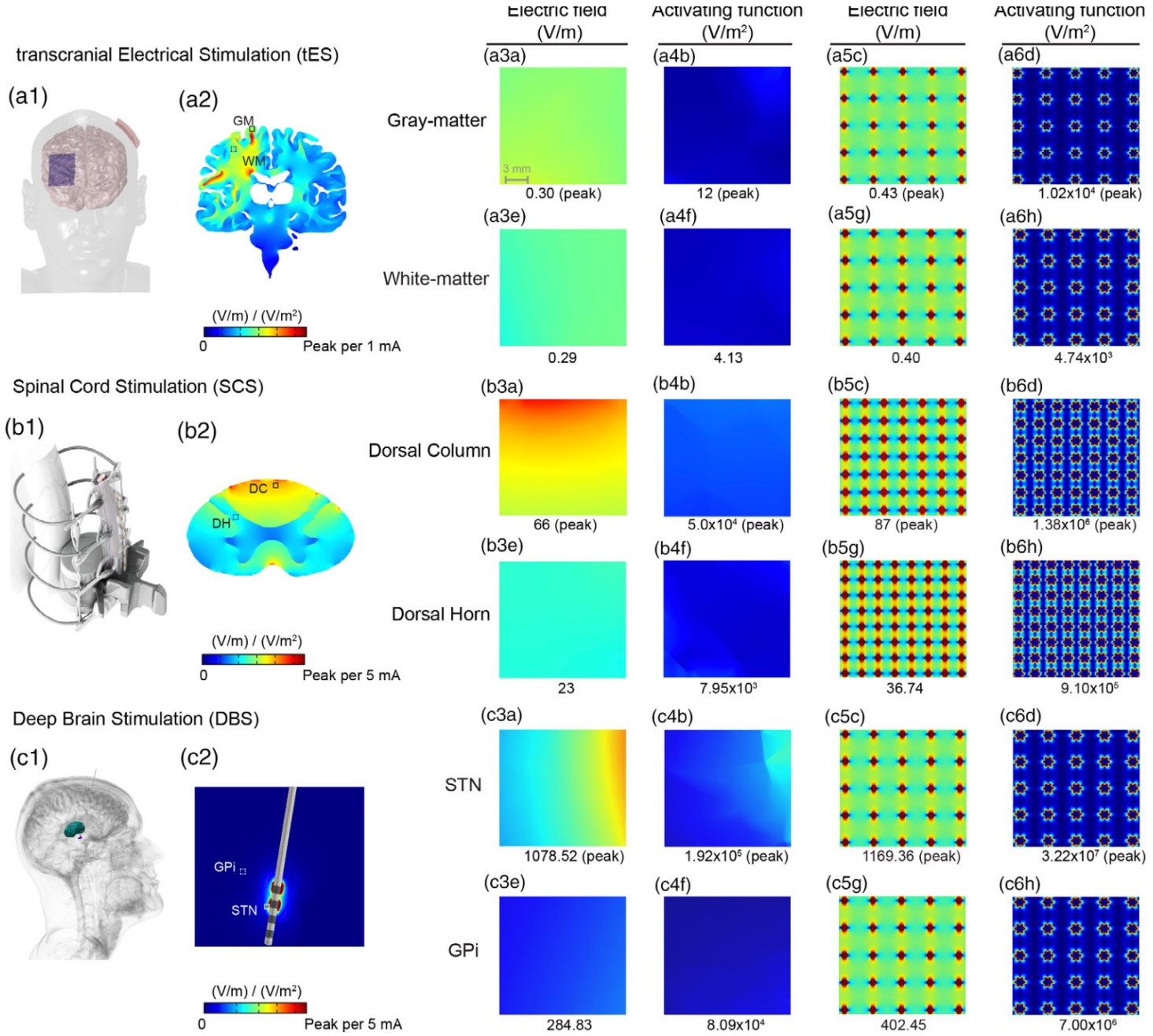
Multi-physics models couple to treatment mechanisms (eg. fluid clearance).

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

Neurocapillary-modulation

Third aspect: Fundamentally changing how neurons are directly stimulated

.



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