Neuromodulation though BBB stimulation or Heating: New Mechanisms of DBS, SCS, and tDCS

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Disclosure
The City University of New York: Patents on brain stimulation. Soterix Medical: Produces tDCS and High-Definition tDCS. Boston Scientific: Neuromodulation Scientific Advisory Board GlaxoSmithKline (GSK): Life Science Scientific Advisory Board Board Mecta Halo Neuroscience: Scientific Advisory Board

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Slides and References @MaromBikson
Novel and Shared Mechanisms of Action across Neuromodulation techniques

- Implants
  - Deep Brain Stimulation (DBS)
  - Spinal Cord Stimulation (SCS)

- In-Hospital
  - Transcranial Magnetic Stimulation (TMS)
  - Electroconvulsive Therapy

- Wearable
  - Transcranial Electrical Stimulation
  - Transcranial Direct Current Stimulation (tDCS)
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• **Neurovascular coupling (unit):** Coupling between brain/spine neuronal activity with vascular flow blood-brain barrier (BBB) permeability.

• **Two way interaction.** Neuronal activity activates vascular (e.g. fMRI), Transport across BBB tightly controlled to regulate brain function.

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**Neuromodulation of neurovascular unit:**

- Brain vasculature changes inevitable secondary to neuronal stimulation (e.g. fMRI changes after brain stimulation)

- Can neuromodulation directly activate endothelial cells of the BBB, leading to secondary neuronal changes
“Primacy” of neurons as targets of neuromodulation means any changes in vascular function assumed secondary to neuron stimulation. **Isolated BBB stimulation established direct neuromodulation.**

- Established BBB model: **cultured endothelium monolayers (BAEC)**

  Water and solute transport quantified

Any uniform electric field generated across BBB model
DBS-relevant electric fields increase hydraulic conductivity of *in vitro* endothelial monolayers.

5 minutes, 200 Hz, 90 us pulse

**Increased water transport across BBB model following 5 min DBS electric field**
DBS-relevant electric fields increase hydraulic conductivity of *in vitro* endothelial monolayers

**Figure:**

(A) No stimulation

(C) 125 V/m

ZO-1 tight-junction protein staining

ZO-1 tight junction protein surrounds endothelial cells in control (No stimulation). DBS disrupts continuity (arrows).
DBS-relevant electric fields increase hydraulic conductivity of \textit{in vitro} endothelial monolayers

A) Representative staining at 250 V/m. (B) Unusual case: 250 V/m caused cell death and exceptional 41x- increase in water permeability
• DBS-relevant electric fields increase hydraulic conductivity of in vitro endothelial monolayers
• Increased water transport likely enhances solute transport, impacting neurons
• Dose dependent increase in BBB transport
• Via opening peri-cellular Tight Junctions.

• No evidence for cell electroporation / transmembrane transport.
• Plausible in any brain / spinal structures
• In vitro BBB system may not be good model for long-term (reversible) changes
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**Wearable**
- Transcranial Electrical Stimulation
- Transcranial Direct Current Stimulation (tDCS)
Transcranial Direct Current Stimulation is a wearable brain stimulator applying Direct Current (no pulses)

(Probably) most investigated interventional neurotechnology
tDSC: transcranial Direct Current Stimulation

Cathode (-)
Electrode

Anode (+)
Electrode

2 mA
20 minute session
Transcranial Direct Current Stimulation (tDCS) of the BBB

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

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Suppression and Control of Epileptiform Activity by Electrical Stimulation: A Review

DOMINIQUE M. DURAND, MEMBER, IEEE, AND MAROM BIKSON
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 (e.g. fMRI, fNIRS) but considered epiphenomena
Direct current stimulation of endothelial monolayers induces a transient and reversible increase in transport due to the electroosmotic effect

• BBB model: isolated cultured endothelium monolayers
• Water and solute transport quantified
• Direct Current electric field generated across BBB model
• Computational model of tight junction
Direct current stimulation of endothelial monolayers induces a transient and reversible increase in transport due to the electroosmotic effect.
Induced water transport across BBB model linear with direct current intensity
Direct current stimulation of endothelial monolayers induces a transient and reversible increase in transport due to the electroosmotic effect.

Direct Current stimulation enhances Dextran (70 kDa) but not TAMARA (430 Da) transport across BBB model.
DCS of isolated-BBB increases in transport due to electroosmosis

- Water transport linear with intensity (polarity), as predicted by analytical electroosmosis model (pore equation)
- Solute transport relatively enhanced for larger molecules.
- Gene expression changes (VEGF)
- Electric field across BBB that matters
Transcranial Direct Current Stimulation (tDCS) of the BBB

- Blood (0.7 S/m) more conductive than brain (0.2 S/m). BBB is highly resistive (6.6E-6 S/m) but very thin (1 uM).
- Vasculature provides conductive path leading to high electric fields across BBB (~700 V/m) per 1 V/m in brain
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kHz Spinal Cord Stimulation (SCS)

Implants

In-Hospital

Wearable
What does kHz-rate stimulation challenge conventional models of electrical stimulation mechanisms?

- Neuromodulation stimulation at frequencies (1-10 kHz) above conventional techniques (~100 Hz)
- High rate stimulation require short pulse durations (e.g. 10 kHz : 40 uS)

Because of the low-pass properties of neuron membranes, kHz stimulation “not effective”

- We tested the most established CNS animal model to detect electrical stimulation to measure (any) response to kHz stim: **acute brain slice**
Data from acute rat brain slice model:

- Isolated "column scale", **small intact network**
- The most studied system to study acute (short term) and lasting (plasticity) changes in **synaptic function** and **neuronal excitability**
- Intracellular Recording: **membrane polarization** by electrical stimulation – primary mode of stimulation transduction
- Extracellular evoked **synaptic Current** – very broad sensitivity to change in pre or post-synaptic function
- The most studied system for cellular effects of electrical stimulation
- **If electrical stimulation does something to cells, it should be quantifiable (detectable) in a brain slice**
Neuronal membrane low-pass filter: Shown by Step-response

Stimulation with step-response (long pulse) quantifies membrane time constant result: charging delay

Optical imaging with voltage sensitive dye in rat hippocampal slice:

Effects of uniform extracellular DC electric fields on excitability in rat hippocampal slices in vitro

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~10 ms time constant
Neuronal membrane low-pass filter: Shown by Step-response

Dual soma and bleb (axon terminal) patch

~1 ms time constant
No change in synaptic efficacy or oscillations by 10 kHz stimulation

>300 slices: Positive control (DC field) in every slice. 10 kHz does “not work”

- Rather than consider action potential generation (supra-threshold), consider modulation of ongoing activity (sub-threshold stimulation)
- Weak modulation of oscillations by high-intensity 1 kHz sinusoid, not 10 kHz
No effects of 10 kHz electric fields on brain slice excitability

- Membrane time constant of soma and axons appear too long (1-20 ms) to respond to high-rate pulse widths (> 40 us)
- No evidence for change in synaptic efficacy or excitability
- Results limited to brain slice (avascular, bath temperature control)

Looking for mechanisms of action for kHz therapies: non-conventional mechanisms of action (absent in brain slice)
What does kHz-rate stimulation challenge conventional models of electrical stimulation mechanisms?

- Stimulation a high-rates (1-10 kHz) that are higher then conventional techniques (~100 Hz)
- High rate stimulation also means short pulse durations (e.g. at 10 kHZ : 40 uS)
- Because of the low-pass properties of neuron membranes, high-rate stimulation is "not effective"
- Amount of heat deposited in tissue can increase at high-rate as duty cycle increases ("pulse compression")
Temperature increases by kilohertz frequency spinal cord stimulation

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Tissue Temperature Increases by a 10 kHz Spinal Cord Stimulation System: Phantom and Bioheat Model

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Temperature mapping around SCS lead in phantom

Amount of heat deposited in tissue independent of sinusoidal frequency, sensitive to phantom electrical and thermal conductivity
Temperature increase tracks RMS independent of waveform

- Sine Wave
- Square Wave
- 10 kHz SCS: 40
  us: 10 us: 40 us

\[
I_{RMS} = \sqrt{\frac{1}{T} \int_0^T I(t)_{peak}^2 \, dt} \\
= I(t)_{peak} \sqrt{\frac{t}{T}} \\
= I_{peak} \sqrt{D}
\]
Realistic Anatomically Detailed Open-source SCS (RADO-SCS) Model

neuralengr.org/spinal-cord-stimulation

SCS E-Field and Bioheat FEM model

Compartment electrical, thermal conductivity, blood perfusion metabolism

\[ \rho C_p \nabla T = \nabla \cdot (\kappa \nabla T) - \rho_b C_b \omega_b (T - T_b) + Q_{\text{met}} + \sigma |\nabla V^2| \]
Simple power-law predicts tissue heating during SCS

**Power-law fit:**

\[ \Delta T = A \times \text{RMS}^B \]

\( \Delta T \): Peak temperature increase at given spinal tissue

**RMS:** Waveform power

**A, B:** Constants depend on electrode montage and all tissue properties (especially epidural fat therapy and electrical conductivity)
Temperature Increases by kHz rate Spinal Cord Stimulation (and High-Density SCS and kHz Deep Brain Stimulation)

- kHz SCS deposits much more power in tissue compared to conventional SCS frequencies, reflecting increased duty cycle. (Fully explains IPG battery run down)
- Only waveform power (RMS) determines temperature increases
- ~0.5 °C during clinical relevant kHz-rate SCS parameters
- Did not model metabolic or other dynamic tissue response to SCS
- Tissue heating will impact short and long-term outcomes
- Relevant to “High Density” SCS waveforms per RMS
- IPG bandwidth and voltage compliance throttle heating
- Relevant to 10 kHz DBS (subject to encapsulation layer conductivity)

Zannou, Khadka, Truong, Zhang, Esteller, Hershey, Bikson. Temperature Increases by kilohertz frequency SCS. Brain Stim. 2018
Zannou, Khadka, Truong, FallahRad, Kopell, Bikson. Tissue Temperature Increases by 10 kHz SCS System. Neuromodulation 2019
Khadka, Harmsen, Lozano, Bikson et al. Bioheat model of kHz Deep Brain Stimulation increases in brain tissue temperature. In Review
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