Advances in Transcranial Direct Current Stimulation in Psychiatric Disorders. April 17, 2021
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
Mecta, Biovisics, Humm, Halo Neuroscience, Google X, i-Lumen, Biovisics

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Slides and References @MaromBikson
Neuromodulation technologies platforms vary in how energy is delivered to what target.
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Implants

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

In-Hospital

- Transcranial Magnetic Stimulation (TMS)
- Electroconvulsive Therapy

Wearable

- Transcranial Electrical Stimulation (tES)
- Transcranial Direct Current Stimulation (tDCS)
Transcranial Direct Current Stimulation (tDCS) is a wearable brain stimulator applying Direct Current (no pulses)

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

- **Cathode (-) Electrode**
- **Anode (+) Electrode**

- 2 mA
- 20 minute session
- Mild tingling sensation
- No overt brain response

"Anodal" / "Cathodal" refer to proximity of target
"Cathodal" tDCS
Soma hyper-polarized
Brain function “dampened”

"Anodal" tDCS
Soma depolarized
Brain function ”boosted”

Radman et al. Role of cortical morphology in uniform electric field stimulation. Brain Stim. 2013
Individualized high-resolution MRI

Segment tissues (skin, skill, CSF, brain) in model

Place electrodes (in model) and predict current flow through head

For a given head anatomy, a given electrode placement, where in the brain does current go?

Datta et al. Gyri-precise model of tDCS/ Brain Stimulation 2009
M1-SO tDCS

Brain Activation
Maximum
Moderate
Minimum
(Electric Field)

Datta et al. Gyri-precise model of tDCS/ Brain Stimulation 2009
M1-SO tDCS

Datta et al. Gyri-precise model of tDCS/ *Brain Stimulation* 2009
High-Definition tDSC – 4x1

Datta et al. Gyri-precise model of tDSC/ Brain Stimulation 2009
High-Definition tDCS – 4x1

Datta et al. Gyri-precise model of tDCS/ Brain Stimulation 2009
“4x1” montage of High-Definition tDCS

- Total of 5 small “HD” electrodes (4+1)
- Center electrode over target determines polarity 4 return electrodes
  - “Ring” radius determines modulation area

![Diagram of brain and electrodes with color-coded currents](image)

- Center electrode: CATHODE
- Center electrode: ANODE

- Outward current (inhibitory)
- Inward current (excitatory)
It is well established: Direct Current stimulation is a powerful modulatory of ongoing plasticity
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Direct current stimulation boosts hebbian plasticity in vitro

Greg Kronberg*, Asif Rahman ¹, Mahima Sharma, Marom Bikson, Lucas C. Parra

Brain Stimulation 13 (2020) 287–301
Non-invasive Neuromodulation / tDCS
Going home (in the time of COVID)
Transcranial electrical stimulation (transcranial Direct Current Stimulation) and transcutaneous Auricula Vagus Nerve Stimulation (taVNS)

From in-clinic to "Remote-Supervised" Neuromodulation platform.
Remotely-supervised transcranial direct current stimulation (tDCS) for clinical trials: guidelines for technology and protocols

Leigh E. Charvet1*, Margaret Kasschau1, Abhishek Datta2, Helena Knotkova3, Michael C. Stevens4, Angelo Alonzo5, Colleen Loo5, Kevin R. Krull6 and Marom Bikson7

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Guidelines for TMS/tES clinical services and research through the COVID-19 pandemic

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Expertise of operator

Home-use
Self application
or Supervised

Clinic
Trained operator

Medical center
or University
Increased automation

**Home:** Fully automatic, No flexibility

**Clinic:** Semi-automatic, Some flexibility

**Medical Center:** Customization, flexibility, integration with other equipment
Is more risk acceptable in any case?

How we remotely regulate stimulation and monitor compliance and outcomes

Manage Risk

Home  Clinic  Medical Center
Imaging integrated with Neuromodulation (at home)

- functional Near Infrared Spectroscopy
- Mobile EEG and physiology
FDA IDE trial: tDCS-LTE for Depression

- Motivated in part by limited access FDA approved in-clinical treatments (rTMS, ECT)
- Home-based transcranial Direct Current Stimulation Limited-Total-Energy platform (TDCS\textsuperscript{LTE})
- Device: Remote control of dosing and compliance monitoring
- Contactless
- First center: NYU Langone
- Mix of automated (ElectraR\textsubscript{x}) symptom monitoring and telemedicine
taVNS for “long neuro-COVID”

• Subjects who are post COVID but experience any lasting (new) neurological or psychiatric symptom. Center: MUSC

• Device: Remote control of dosing and compliance monitoring

• tAVNS dual action: parasympathetic activation + direct brain modulation

• Contactless

• Integrated remote real-time physiology monitoring (HR, oximeter)

• Mix automated (ElectraRx) symptom monitoring and telemedicine
Neurovascular Modulation
Neurovascular Modulation
Changes everything about current flow modeling.
A new therapeutic target for old indications.
Acute neuro-protection.
tDCS may have powerful direct effects on brain vasculature

(the most obvious effect of tDCS is skin reddening under the electrode. Could the brain be “reddening”?)
• **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

**tDCS 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**
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
“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
Direct current stimulation of endothelial monolayers induces a transient and reversible increase in transport due to the electroosmotic effect.

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

tDCS enhances drug transport

+ Gene expression changes (VEGF)
• During tDCS current is “funneled” into and through blood vessels
• Resulting in very high electric field across the vessel walls: the blood-brain-barrier (BBB)
• tDCS produces ~1 V/m around neurons and >150 V/m across BBB
tDCS may have powerful direct effects on brain vasculature

Govern "boosting" of brain function and efficacy in neurorehabilitation

Potential protective role (acute stroke)
Neurovascular Modulation is a new therapeutic target for old indications

Electroosmosis: tDCS (and other neuromodulation techniques) directly enhances water and molecule transport across the BBB, independent of actions of neurons.

Cancel LM, Arias K, Bikson M, Tarbell JM (2018). Direct current stimulation of endothelial monolayers induces a transient and reversible increase in transport due to the electroosmotic effect. Scientific Reports,


Brain clearance: tDCS boosts transport across extracellular space.

Neurovascular Modulation: Acute Neuroprotection
Neurovascular Modulation: Acute Neuroprotection

(1) Immediate decreases in excitability
+ (2) Increases neurovascular function.


Transcranial Direct Current Stimulation as a Neuroprotection in Acute Stroke (TESSERACT)
ClinicalTrials.gov Identifier: NCT03574038
Mersedeh Bahr Hosseini, MD, University of California, Los Angeles
Patients received image-guided injury-specific (salvageable penumbra) 4x1 HD-tDCS. Cathode center (inhibit neurons), Anode ring (boost blood flow)
Neuronal Network Oscillations
Sensitivity of oscillating neuronal networks to Temporal Interference Stimulation

Deep in the brain Amplitude-Modulated (AM) kHz electric fields are generated. Fixed amplitude kHz electric field at superficial cortex.
Sensitivity of oscillating neuronal networks to Temporal Interference Stimulation

Stimulation of gamma-oscillations in brain slice + neuronal-network model. High sensitivity to low frequency stimulation (5 Hz).

AM kHz electric field modulate the amplitude of oscillations (Dynamic Modulation). Unmodulated kHz fields enhance oscillations (Static Modulation).

Esmaeilpour Z, Kronberg G, Reato D, Parra LC, Bikson M. Temporal interference stimulation targets deep brain regions by modulating neural oscillations Brain Stimulation 2020 *in press*
Sensitivity of oscillating neuronal networks to Temporal Interference Stimulation

C.1) $I = 83 \text{ mA (Model } T_m = 0.4 \text{ ms)}$

C.2) $I = 138 \text{ mA (Model } T_m = 1 \text{ ms)}$

C.3) $I = 222 \text{ mA (Model } T_m = 3 \text{ ms)}$

Best Practices and Latest Developments in tDCS

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