ENGINEERING
PERSONALIZED
NEUROMODULATION

Marom Bikson
Disclosure (relevant to presentation)


Support

Neuromodulation

Application of energy, often electricity, to the body on purpose (to restore or enhance function)
What defines neuromodulation technologies is how energy is delivered to what target.

- 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)
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- **Implants**
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  - Spinal Cord Stimulation (SCS)

- **In-Hospital**
  - Transcranial Magnetic Stimulation (TMS)
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- **Wearable**
  - Transcranial Electrical Stimulation (tES)
  - Transcranial Direct Current Stimulation (tDCS)
tDCS: Transcranial Direct Current Stimulation

- Hand-held device, head gear
- 20 minute session, 2 mA via scalp electrodes
- Modulator of brain excitability and plasticity
- > 400 controlled trials across neurological / psychiatric inductions + performance
- Remote supervised (home)
1) Century of clinical testing, poor reproducibility:


tDCS: Transcranial Direct Current Stimulation

- Mixed clinical results
- Too many indications
- Too low intensity to trigger neuronal firing
- Direct current is not a physiologic signals
- Not spatially target
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tDCS

Experimentally-verified Anatomical MRI derived models of current flow
tDCS

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Circuit therapeutics
Experimentally-verified Anatomical MRI derived models of current flow
tDCS: Experimentally-verified Anatomical MRI derived models of current flow

High Definition tDCS

Circuit therapeutics
tDCS

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tDCS

High Definition tDCS

Experimentally-verified Anatomical MRI derived models of current flow

Circuit therapeutics

Non-invasive electrical targeting
• Software allows you to steer currents to targeted brain regions
• Single programmable device and head-gear
• Target optimized solved. Question is what target?

Identify target
Select current per electrode
1) **Focal transcranial**: Datta et al. Gyri-precise model of tDCS: Improved spatial focality using ring. Brain Stim 2009

2) **Small (HD) electrodes**: Minhas et al. Electrodes for high-definition DC stimulation. J. Neurosci Methods 2010

3) **Closed-form optimization (deep)**: Dmochowksi et al. Optimized multi-electrodes stimulation increases focality and intensity at target. J Neural Engr 2011

4) **Model validation**: Huang et al. Measurements and models of electric fields in the human brain during transcranial electric stimulation. Elife 2017
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**High-intensity Pulses**

- Over-driving a neural network

**Low-intensity DC**

- Neuromodulation comes from secondary non-linear changes
Over-driving a neural network

High-intensity Pulses

Low-intensity DC
Over-driving a neural network
Interacting with specific activity in a neural network (Neuromodulation)

High-intensity Pulses

Over-driving a neural network

Low-intensity DC

Transcranial Direct Current Stimulation (tDCS)
Network of interest (e.g. depression, math cells)

Other networks – not targets for neuromodulation

Electrode

Current flow across entire brain region

Preferential modulation of more active network (activity dependent)
Functional Targeting:
Activity dependent sensitivity to brain stimulation
Theta Burst Stimulation (TBS) generates LTP which is modulated by concurrent Direct Current Stimulation (DCS)

LTP from theta burst stim + Cathodal or Anodal Direct Current Stimulation
Theta Burst Stimulation (TBS) generates LTP which is modulated by concurrent Direct Current Stimulation (DCS)

- DCS does generate synaptic plasticity de novo (Activity Dependent)
- Directions of changes by anodal/cathodal depends on LTP types
Repeated DCS accelerates LTP and boosts the ceiling for synaptic learning

- Hypothesis: Combing DCS with ongoing training enhances the rate and ceiling learning specifically of that task (Activity Dependent)
tDCS applied with a task. Specificity comes from the task. tDCS makes the task (therapy) more effective
Novel cellular targets of tDCS support Functional Targeting Coupled Neuro-Vascular Hypothesis of Neuromodulation
tDCS papers, low intensity modulation

1) Decades of mechanistic studies in animals (original LTP):

2) How much neurons polarize:
   Radman et al. Role of Cortical Cell Type and Morphology in Electric Field Stimulation. Brain Stimul. 2009

3) Modulation of oscillations:

4) Neuro-vascular Coupling:
   Cancel et al. Direct current stimulation of endothelial monolayers induces increase in transport due to the electroosmotic effect. Nature Sci Reports. 2018
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The challenge for tDCS is not feasibility, but optimization to meaningful applications
• Software allows you to steer currents to target brain region
• Single programmable device and head-gear
• Target optimized solved. Question is what target?
Maybe one size does not fit all?

What is biomarker?

What is intensity?

What is inclusion?

What is the timing?

What is the task?

• Target optimized solved. Question is what target?
Personalized Therapy
Personalized Therapy Iterative
Personalized Therapy

- Tunable
- Fast Iterations
- Minimal risk
Personalized Therapy

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Drugs
Molecular

Implants
In-Hospital

Apps

Wearable
neuromodulation
Personalized Therapy

- Effective
- Tunable
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Drugs
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neuromodulation
Software allows you to steer currents to targeted brain regions

- Single programmable device and head-gear
- Target optimized solved. Question is what target?
EEG automatically and instantly “inverted” to optimal HD-tDCS montage

- Decades old “reciprocity” hypothesis, but with closed head model
- Activity guided targeting, does not require source localization
Phase II (Harvard/Spaulding) Fibromyalgia pain
Daily in-clinic sessions of EEG Guided HD-tDCS, open label
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Daily in-clinic sessions of EEG Guided HD-tDCS, open label
Targeted (Image Guided) tDCS

2) EEG + HD-tDCS Fibromyalgia: Castillo-Saavedra et al. Clinically Effective Treatment of Fibromyalgia With High Definition tDCS. J Pain 2016
3) EEG to HD-tDCS reciprocity: Dmochowski et al. Optimal use of EEG recordings to target active brain areas with transcranial electrical stimulation. Neuroimage 2017
Personalized Neuromodulation Therapy at Home
Personalized Neuromodulation Therapy at Home

Head-gear ($R_x + $ sensors)

App

Medical wearable

3x Measure

decision

Historical data
ElectraRx – Prescription

Adaptive questions optimized to select daily treatment (not diagnose)

What is bothering you?
How are you?
What kind of pain?
How’s work?

Option 1 Rx
Option 2 Rx
Adaptive Questionnaires for Personalized Neuromodulation
Adaptive Questionnaires for Personalized Neuromodulation

I'm sorry to hear that. Can you tell me what is bothering you? (click all that apply)

- Anxiety
- Sadness
- Pain
- Headache
- Lack of focus
- Lack of energy
- Lack of appetite
- Lack of sleep
- Ringing or buzzing in the ears

Is there anything else you would like me to share with your doctor?

Continue
Adaptive Questionnaires for Personalized Neuromodulation
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Adaptive questions optimized to select daily treatment (not diagnose)

How are you?
What is bothering you?
What kind of pain?
How’s work?

Option 1 Rx
Option 2 Rx
Personalized Neuromodulation Therapy at Home

- Head-gear ($R_x +$ sensors)
- App
- Medical wearable

Decision

Historical data

Measure $3x$
Responsive Measures for Personalized Neuromodulation

- Head gear – EEG, EOG, fNIRS, GVS
- HealthDot Sensors - PPG, ECG, Respiration, IMU, EDA, EMG

HealthDot (chronic)
Headgear (during session)

[ Raw data ]
Vital sign
Brain measures

Option 1 Rx
Option 2 Rx
Personalized Neuromodulation Therapy

Fast Iterative

Tunable targeted

Head-gear ($R_x +$ sensors)

App

Medical wearable

Measures

Responsive Adaptive Q

[Raw Data]

Historical data

decision
tDCS applied with a task. Specificity comes from the task. tDCS makes the task (therapy) more effective.
Personalized Neuromodulation Therapy

Fast Iterative

Tunable targeted

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App

Medical wearable

Measures

Decision

Historical data

Responsive Adaptive Q [Raw Data]
Personalized Neuromodulation is Personalized
Personalized home-based tDCS


2) **Pediatric Epilepsy:** Meiron et al. HD-tDCS in early onset epileptic encephalopathy. J Brain Inj 2017

2) **Multiple Sclerosis:** Kasschau et al. tDCS Feasible for Remotely Supervised Home Delivery in MS. Neuromod 2016

3) **Dry tDCS:** Khadka et al. Tolerability of a novel multilayer hydrogel composite non-adhesive electrode for transcranial direct current stimulation. Brain Stim. 2018
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