Disclosure

The City University of New York has patents on brain stimulation with Marom Bikson as inventor.

Marom Bikson was equity in Soterix Medical Inc.

Marom Bikson serves on the Boston Scientific neuromodulation scientific advisory board.
Toward Markers of Target Engagement in tDCS

Engineering and cellular principles supporting specificity of outcomes

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INS Pre-Conference: Non-invasive brain stimulation.
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Transcranial Direct Current Stimulation (tDCS)

• Non-invasive, portable (9V), well-tolerated neuromodulation.
• Low-intensity (mA) current passed between scalp electrodes.
• Tested for cognitive neuroscience and neuropsychiatric treatment and neurorehabilitation.

Ø How can a 9V battery do anything for the complex brain?
Ø How is specificity of action achieved?

Very abbreviated list of tDCS indications and applications:
Depression, Pain, Migraine, Epilepsy, PTSD, Schizophrenia, Tinnitus, Neglect, Rehabilitation (motor, aphasia), TBI, OCD, Attention / Vigilance, Accelerated learning (reading, motor skills, math, threat detection), Memory, Creativity, Sleep (SW, Lucid dreaming, Threat detection, Impulsivity, Compassion, Jealousy, IQ, Prejudice...
Target Engagement

- How can a 9V battery do anything for the complex brain?
- How is specificity of action achieved?
Target Engagement

- How can a 9V battery do anything for the complex brain?
- How is specificity of action achieved?

Through **anatomical targeting** of specific brain regions.

Can be studied using computational models of current flow.
tDCS electrode position on the head determines which regions are stimulated

(?) Specific brain regions are associated with specific functions / disease

Truong et al. Clinician accessible tools for GUI computational models. “BONSAI” and “SPHERES”. Brain Stimulation 2014
"Cathodal" tDCS
Soma hyper-polarized
Apical dendrite depolarized

"Anodal" tDCS
Soma depolarized
Apical dendrite hyper-polarized

tDCS electrode position on the head determines which regions are stimulated

(!) Must consider both anode and cathode electrodes

Datta et al. Electrode montages for tDCS: Role of "return" electrode Clinical Neurophys. 2010
High-Definition tDCS uses arrays of electrodes to focus current to targets. Software allows you to generate subject and target specific tDCS “formulation”.

“4x1” montage of High-Definition tDCS

(!) Non-invasive electrical targeting of cortex

Datta et al. Gyri-precise model of tDCS: Improved spatial focality using a ring versus conventional pad. *Brain Stimulation* 2009
Target Engagement

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Target Engagement

- How can a 9V battery do anything for the complex brain?
- How is specificity of action achieved?

Through **functional targeting** of specific brain regions.

Can be studied using brain slices models of synaptic efficacy and plasticity.
From Anatomical Targeting to Task Targeting

Network of interest (e.g. depression, pain network)  Other networks – not targets for neuromodulation

Current flow across entire region

Preferential modulation of selected active neurons

Bikson et al. Origins of specificity during tDCS. *Front Human Neuro* 2013
Synaptic efficacy is modulated by Direct Current (polarity specific)

Synaptic efficacy is modulated by Direct Current (polarity specific)

- Direct Current stimulation does not generate synaptic activity or neuronal firing (Functional Targeting)

Direct Current has sustained effects on synaptic efficacy despite synaptic depression

- While Direct Current stimulation is on, ongoing synaptic activity boosted (Functional Targeting)

Theta Burst Stimulation (TBS) generates LTP which is modulated by concurrent Direct Current

LTP from theta burst stim

“Cathodal” or “Anodal” Direct Current Stimulation

EPSP

Theta Burst Stimulation (TBS) generates LTP which is modulated by concurrent Direct Current

- Direct Current stimulation does not itself generate synaptic plasticity (Functional Targeting)

Repeated stimulation accelerates LTP and boosts the ceiling for synaptic learning

- Hypothesis: Combing Direct Current stimulation with repeated training of a task may enhance the rate and ceiling learning of that task (Functional Targeting)
Through **anatomical targeting** of specific brain regions.

- Can be studied using computational models.

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Through **functional targeting** of specific brain networks.

- Can be studied using brain slices models.
Target engagements matters to understand mechanism and for intervention optimization
How can tDCS be optimized?

- For translation, models are only useful in predicting outcomes.
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**Computational models for anatomical targeting of brain regions.**

**Animal models for functional targeting of specific brain activity**
How can tDCS be optimized?

- For translation, models are only useful in predicting outcomes.

Computational models for anatomical targeting of brain regions.

Animal models for functional targeting of specific brain activity.

- Sophisticated tDCS optimization now integrated anatomical and functional targeting.
"Cathodal" tDCS
Soma hyper-polarized
Apical dendrite depolarized

"Anodal" tDCS
Soma depolarized
Apical dendrite hyper-polarized

Synapses are on both depolarized and hyper-polarized compartments.

Axon terminals are also polarized.

High Rate Stimulation generates LTP which is modulated by concurrent Direct Current

High Rate Stimulation generates LTP which is modulated by concurrent Direct Current

- Depolarized dendrites boost plasticity, under anodal or cathodal DCS

Computational models for anatomical targeting of brain regions.

Animal models for functional targeting of specific brain activity

- Sophisticated tDCS optimization now integrated anatomical and functional targeting.

Interactions between stimulation polarity and activated network determining modulation

• Any EEG can be automatically “inverted” to an optimal HD-tDCS montage


- 50% reduction in VAS Pain + EEG Pain markers in 1/2 subjects within two weeks of optimization
Computational models for anatomical targeting of brain regions.

Animal models for functional targeting of specific brain activity

- Sophisticated tDCS optimization now integrated anatomical and functional targeting.

✓ Activity guided targeting. Integrated + Automatic. Feedback based on hypothesis of reciprocity.

Target engagement in tDCS (and neuromodulation)

- Medical center: Transition from sponge-pad tDCS to High-Definition tDCS (HD-tDCS), with image-guided targeting. Individualized through close-loop.

- Home based: Extended therapy (repeated sessions) with “wearable guided targeting” + big data

- Training based functional targeting, moving beyond brain-as-a-sliding-scale models (e.g. anode = ‘up’).

Collaborators:

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Felipe Fregni, Ziv Peremen, Amir Geva, Leigh Charvet, John Jefferys

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Slides and References at NeuralEngr.com
Extra Slides
Home-based extended therapy with
1) task-control (engage network) +
2) integrated wearables (feedback targets engaged networks)
Electric fields modulate both strong and weak synapses, input specifically.
Electric fields enhance stronger synapses more than weak synapses during synaptic learning.
tDCS: Sustained AXON TERMINAL weak polarization