A dialogue with the cerebral cortex. Barcelona 2015

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Modulating Brain Processing and Learning with Non-Invasive Electrical Stimulation

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Disclosure:

Soterix Medical Inc. produces tDCS and High-Definition tDCS. Marom Bikson is founder and has shares in Soterix Medical. Some of the clinical data presented may be supported by Soterix Medical. Marom Bikson serves on the scientific advisory board of Boston Scientific Inc.

Support:

NIH (NINDS, NCI, NIBIB), NSF, Epilepsy Foundation, Wallace Coulter Foundation, DoD (USAF, AFOSR)
What is Neuromodulation?

• Application of electricity to change brain function
• “Electroceuticals”
• Many techniques: Name of each method is defined by how electricity is delivered
  (some letters ending with “s”).

Deep Brain Stimulation (DBS)
Transcranial Magnetic Stimulation (TMS)
Transcranial Direct Current Stimulation (tDCC)
Why Neuromodulation?

- To probe the brain for science
- To treat the brain: neurological, psychiatric, rehabilitation
- To enhance mental performance (neuro-enhancement)

Deep Brain Stimulation (DBS)  Transcranial Magnetic Stimulation (TMS)  Transcranial Direct Current Stimulation (tDCS)
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.

How can a 9V battery do anything for the complex brain?
How is specificity of action achieved?
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tDCS Publications
- Depression, pain, migraine, epilepsy, PTSD, schizophrenia, narcolepsy, neglect, rehabilitation (motor, aphasia), TBI, OCD, addiction, Accelerated learning (reading, motor skills, math, threat detection), memory, creativity, lucid dreaming…
How could Pharmaceuticals treat so many disorders?
It’s not one thing.
Many formulations.

How could Electroceuticals (tDCS) treat many disorders?
It’s not one thing.
Many “formulations”.
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
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

✓ Allows targeting of selected cortical regions

High Definition tDCS for Stroke Rehabilitation

Dmochowski et al. Targeted transcranial direct current stimulation for rehabilitation after stroke. *Neuroimage* 2013
tDCS montages for treatment of Depression

- Brunoni et al.
  - SELECT / ELECT
  - target: DPLPC
  - 2.0 mA
  - Double blind RCT

- Loo et al.
  - Multi-Center Trial
  - target: DPLPC
  - 2.5 mA
  - Double blind RCT

- Target stimulated but not specifically

Seibt al. The pursuit of DLPFC. *Brain Stimulation* 2015
Transcranial Direct Current Stimulation (tDCS)

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, Lucid dreaming, Threat detection, Impulsivity, Compassion…

Majority of trials use diffuse tDCS

- How can a 9V battery do anything for the complex brain?
- How is specificity of action achieved?
How could weights help with so many sports?  
It’s a tool to enhance specific training.

How could Electroceuticals (tDCS) treat many disorders?  
It’s a tool to enhance cognitive training and therapy.
tDCS is a tool for the mind that enhances activity and plasticity from cognitive training and therapy

- Human trials with tDCS use brain stimulation as adjunct to the brain training (e.g. math, game)
- Changes in mood that facilitate training (vigilance, relaxation)
- Boosting placebo – real and specific physiological response associated with expectation

Schambra et al. It’s all in your head: reinforcing the placebo response with tDCS. Brain Stimulation 2014
How does tDCS just enhance the trained task?

Cellular mechanism: Functional Targeting

From Anatomical Targeting to Functional Targeting
From Anatomical Targeting to Functional Targeting

Network of interest (e.g. depression, math cells)

Other networks – not targets for neuromodulation

Preferential modulation of selected active network (activity dependent)

Current flow across entire region
Supra and sub-threshold electrical stimulation
Supra and sub-threshold electrical stimulation

**High-intensity Pulses**

- Over-driving neurons (axons)
- Neuromodulation (therapy) derives from secondary system changes

**Low-intensity Direct Current**

TMS

Invasive cortical

DBS
Supra and sub-threshold electrical stimulation

**High-intensity Pulses**
- Over-driving neurons (axons)
- Neuromodulation (therapy) derives from secondary system changes

**Low-intensity Direct Current**
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**Low-intensity Direct Current**
**Supra and sub-threshold electrical stimulation**

**High-intensity Pulses**
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**Low-intensity Direct Current**
- Polarize neurons
- Neuro-modulation: Interacting with specific ongoing neuron activity

**tDCS**
1. tDCS produces a sustained weak polarization of neuronal membranes

2. Weak polarization modulates synaptic efficacy
① tDCS produces a sustained weak polarization of neuronal membranes

② Weak polarization modulates synaptic efficacy
Direct Current
tDCS: Sustained weak polarization

Brain slice: Optical Mapping with Voltage Sensitive Dyes

Bikson et al. Effects of uniform extracellular DC electric fields on excitability in rat hippocampal slices. *J Physiol* 2004
Bikson et al. Effects of uniform extracellular DC electric fields on excitability in rat hippocampal slices. *J Physiol* 2004
① tDCS produces a sustained weak polarization of neuronal membranes

② Weak polarization modulates synaptic efficacy
Weak polarization modulates synaptic efficacy

The amount of post-synaptic current for given pre-synaptic activity

Modulation of on-going synaptic activity, not generation

Excitatory post-synaptic currents (field) in brain slice

Weak polarization modulates synaptic efficacy

Excitatory post-synaptic currents (field) in brain slice

Train of synaptic ongoing activity

Direct Current

- Ongoing synaptic activity modulated while tDCCS sustained
- Substrate for plasticity
- Modulation of ongoing activity, *not generation*
Biophysical basis of tDCS functional selectivity

Fritsch 2010: BDNF dependent + activity dependent induction

Specific ongoing synaptic activity (no plasticity)

Ongoing Plasticity

“None-active” synapse

No tDCS synaptic plasticity

Rahman 2015: Pathways specific + plasticity dependent modulation

DC + Theta burst synaptic activity

tDCS induces plasticity

tDCS modulates plasticity

Synaptic Plasticity in brain slice
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Deployable tDCS (keeping is simple)

- Repeated sessions (e.g. weeks) required for efficacy and maintenance.
- Home-based therapy reduces burden on patients (travel) and hospital (cost).
- “Home” technology focused on compliance.