How does transcranial Direct Current Stimulation change cortical processing: Insights from animal models

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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.

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The organization of cortex by columns
The organization of cortex by columns

Cortical columns received information from different brain regions (input) and processes this information (output)
Direct Current stimulation of columns: tDCS

transcranial Direct Current Stimulation

Application of weak Direct Current using electrodes on the scalp: produces Direct Current flow through the cortex

Datta, Bikson et al. Gyri-precise head model of transcranial direct current stimulation. *Brain Stimulation* 2009
Direct Current stimulation of columns: tDCS

How does Direct Current change cortical processing?
All experimental data from acute brain slice of rat cortex of hippocampus:

- No background activity, any synaptic input controlled in a pathway specific manner
- Voltage sensitive dye imaging
- Intracellular recording of identified cells
- Quantification of synaptic function
- Established models of LTD/LTP
- Column-scale systems analysis
Direct Current stimulation of columns: tDCS

How does Direct Current change cortical processing?
Direct Current stimulation of columns: tDCS

Pyramidal Neuron

How does Direct Current change neurons?
Direction of Direct Current relative to column

Anodal

Direct Current

Current direct along main axis of pyramids

Cathodal

Direct Current

Current direction perpendicular
Direct Current stimulation of columns: tDCS

How does Direct Current change neurons?
How does Direct Current change neurons?

Pyramidal Neuron

- No Direct Current
- Anodal Direct Current
- Cathodal Direct Current

Depolarized membrane compartments
Hyper-polarized membrane compartments
How does Direct Current change neurons?

Optical Mapping with voltage sensitive dyes

How does Direct Current change neurons?

Intracellular recording and morphology

Radman, Bikson et al. Role of cortical cell type and morphology in subthreshold and suprathreshold uniform electric field stimulation. Brain Stimulation. 2009
How does Direct Current change neurons?

• tDCS produces direct current in the brain
  ➢ Brain intensity = 0.3 V/m
    Datta, *Brain Stim.* 2009

• Biphasic neuron membrane polarization
  ➢ Only: current parallel to neuron axis
  ➢ Anodal = pyramidal neuron soma depolarization
  ➢ Max 0.3 mV soma polarization per V/m
    Bikson, *J Physiol.* 2004
    Radman, *Brain Stim.* 2009

• During tDCS neuron soma polarize little, maximum <0.1 mV
Direct Current stimulation of columns: tDCS

How does Direct Current change cortical processing?
Direct Current stimulation of columns: tDCS

How does Direct Current change cortical processing?
How does Direct Current change cortical processing?
How does Direct Current change cortical processing?
How does Direct Current change synaptic efficacy?

Pyramidal Neuron

No Direct Current

Anodal Direct Current

Cathodal Direct Current

Depolarized membrane compartments

Hyper-polarized membrane compartments

Pathway Specific Testing
How does Direct Current change synaptic efficacy?

Pathway-specific synaptic efficacy (fEPSP)

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

Cathodal stimulation (soma Hyperpolarized)
Control
Anodal stimulation (soma Depolarized)

How does Direct Current change synaptic efficacy?

- **Pyramidal Neuron**
  - **No Direct Current**: Pathways Enhanced
  - **Anodal Direct Current**: Direct Current Enhanced, Synaptic Pathways Suppressed
  - **Cathodal Direct Current**: Direct Current Suppressed, Synaptic Pathways Enhanced
  - **Direct Current**: Pathways Enhanced
How does Direct Current change synaptic efficacy?

How does Direct Current change synaptic efficacy?

How does Direct Current change synaptic efficacy?

Pyramidal Neuron

Input

Output

Direct Current

How does Direct Current change synaptic efficacy?

• Direct Current parallel to the column
  ➢ Modulates synaptic efficacy consistent with somatic polarization and terminal polarization

• Direct Current perpendicular to the column
  ➢ Modulates synaptic efficacy consistent with terminal polarization

• During tDCS most current is perpendicular
• Terminals are most sensitive to polarization
• ~1% change per V/m Direct Current

How does Direct Current change synaptic efficacy?

How does Direct Current change synaptic efficacy?

1. Direction of Direct Current relative to column
2. Membrane compartments polarized (soma, dendrite, axon)
3. Pathways specific modulation of synaptic efficacy
How does Direct Current change cortical processing?
Direct Current stimulation of ACTIVE columns

How does Direct Current change cortical processing?

Organized oscillations
Reato, Bikson. Low-intensity electrical stimulation affects network dynamics by modulating population rate and spike timing. *J Neurosci*. 2010
Reato, Bikson. Low-intensity electrical stimulation affects network dynamics by modulating population rate and spike timing. *J Neurosci*. 2010
Reato et al. Transcranial electrical stimulation accelerates human sleep homeostasis. PLOS Computation Biology 2013
Direct Current stimulation of ACTIVE columns

How does Direct Current change cortical processing?
Direct Current stimulation of ACTIVE columns

- Direct Current modulates gamma oscillations
- Complex non-linear dose-response explained by computational models capturing dynamics
- Pyramidal neurons polarized, inter-neurons indirectly modulated
- **Direct Current stimulation boosted by active network**

Reato, Bikson. Low-intensity electrical stimulation affects network dynamics by modulating population rate and spike timing. *J Neurosci*. 2010
Reato et al. Transcranial electrical stimulation accelerates human sleep homeostasis. PLOS Computation Biology 2013

**Activity dependent and activity specific**
SUMMARY: Direct Current stimulation of columns

• tDCS produces weak direct current in the brain
  Datta, *Brain Stim.* 2009

• Biphasic neuron membrane polarization
  Bikson, *J Physiol.* 2004

• Pyramidal neurons soma’s polarized < 1 mV
  Radman, *Brain Stim.* 2009

• Axon terminals (inputs) polarize > 1 mV

• Synaptic efficacy modulated, pathway specific

• Oscillations modulated by Direct Current
  Reato, *J Neuroscience.* 2010

• Activity specific modulation
  Reato, *PLOS Comp.* 2013
OK, but what does all this tell us about how tDCS changes behavior?

tDCS tested for many applications. How can such a simple technique do so many different things?

Animal data provides a cellular substrate for how tDCS can produce SPECIFIC changes in complex brain brain.
How could weights help with so many sports?
It’s a tool to enhance specific training.

How could tDCS treat many disorders?
It’s a tool to enhance cognitive training and therapy.
tDCS + Task = Boosting of just the Task
How does tDCS just enhance the trained task?

Cellular mechanism: Functional Targeting

Bikson et al. Origins of specificity during tDCS: anatomical, activity-selectivity, and input-bias mechanisms. *Front Human Neuro 2013*
How does Direct Current change neurons?

Intracellular recording and morphology

0.3 mV polarization

0.1 mV polarization

0 mV polarization

1 V/m Direct Current

Radman, Bikson et al. Role of cortical cell type and morphology in subthreshold and suprathreshold uniform electric field stimulation. Brain Stimulation. 2009
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
Supra and sub-threshold electrical stimulation

High-intensity Pulses

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

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

High-intensity Pulses

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

Low-intensity Direct Current

• Polarize neurons
• Neuro-modulation: Interacting with specific ongoing neuron activity
How does Direct Current change synaptic efficacy?

Pathway-specific synaptic efficacy (fEPSP)

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

Activity dependent and activity specific

Biophysical basis of tDCS functional selectivity

**Fritsch 2010:** BDNF dependent + activity dependent induction

Specific ongoing synaptic activity (no plasticity)

tDCS induces plasticity

**Rahman 2015:** Pathways specific + plasticity dependent modulation

Ongoing Plasticity

tDCS modulates plasticity

“None-active” synapse

No tDCS synaptic plasticity

Synaptic Plasticity in brain slice
Biophysical basis of tDCS functional selectivity

- Repeated theta-burst plasticity
- Repeated theta-burst plasticity with DCS

Boosting of rate and maximum change!
OK, but what does all this tell us about how tDCS changes behavior?

Animal studies: evidence for “Functional Targeting” where only co-activated networks are boosted.

tDCS tested for many applications. How can such a simple technique do so many different things?
tDCS is a tool that enhances ongoing 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
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