Translational aspects of tDCS: from rodents to humans

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Disclosure:

Soterix Medical Inc. produces tDCS and High-Definition tDCS. Marom Bikson is founder and has shares in Soterix Medical. Marom Bikson serves on the Boston Scientific neuromodulation scientific advisory board.
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

transcranial Direct Current Stimulation (tDCS) in humans

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

(epicranial) Direct Current Stimulation in animals

Application of Direct Current using electrodes on the skull or brain surface: produces Direct Current flow through the cortex

Direct Current stimulation of columns

Direct Current Stimulation in brain slices (in vitro)

Application of Direct Current using electrodes across tissue
in vitro: produces Direct Current flow through the cortex

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

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

- **Anodal**
- **Cathodal**

Current direct along main axis of pyramids

Current direction perpendicular
Direct Current stimulation of columns: tDCS

Pyramidal Neuron

Anodal

Cathodal

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
The concept of bipolar polarization in an electric field

The concept if bipolar polarization in an electric field

The concept of bipolar polarization in an electric field

The concept of bipolar polarization in an electric field

- Hyper-polarized cell compartments
- Depolarized cell compartments

Electric Field
The concept of bipolar polarization in an electric field

The concept of bipolar polarization in an electric field

The concept of bipolar polarization in an electric field

**Soma Polarization** = Electric Field \( \times G_{\text{coupling}} \)

Electric Field (per mA)

Soma depolarizing field

Soma depolarizing field (longer duration)

Soma hyper-polarizing field

The concept if bipolar polarization in an electric field

Soma Polarization = Electric Field * $G_{\text{coupling}}$

Anode tDCS produces depolarization of the soma as long as tDCS is applied.

How does Direct Current change neurons?

- **Pyramidal Neuron**
  - **No Direct Current**
  - **Anodal Direct Current**
  - **Cathodal Direct Current**

- **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

- Layer I Interneuron
- Layer II/III Pyramidal
- Layer V/VI Bursting Pyramidal

0 mV polarization

0.1 mV polarization

0.3 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
How does Direct Current change neurons?

• tDCS produces direct current in the brain
  - Brain intensity = 0.6 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 ~0.2 mV
How does Direct Current change cortical processing?
Direct Current stimulation of columns: tDSC

How does Direct Current change cortical processing?

0.2mV polarization does not produce action potentials.
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
Pathway-specific synaptic efficacy (fEPSP)

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

How does Direct Current change synaptic efficacy?

Pyramidal Neuron

No Direct Current

Anodal Direct Current

Cathodal Direct Current

Direct Current

Pathways

Enhanced

Suppressed

Suppressed

Enhanced
How does Direct Current change synaptic efficacy?

How does Direct Current change synaptic efficacy?


How does Direct Current change synaptic efficacy?
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

Direct Current stimulation of ACTIVE columns

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

Pyramidal Neurons

Inter-neurons

Direct Current

Organized oscillations

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

Column network gamma oscillations

Brain Slice

Network Model

Voltage

Time (s)

0 0.2 0.4 0.6 0.8 1

0 0.2 0.4 0.6 0.8 1

Acute adaptation

Anodal Cathodal

Power modulation

Gamma oscillations power change (%)

0 50 100

-50 0 50

Time (s)

0.5 1 1.5 2 2.5 3 3.5 4 4.5

Reato, Bikson. Low-intensity electrical stimulation affects network dynamics by modulating population rate and spike timing. J Neurosci. 2010
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

- **Long-lasting changes in oscillation power**
- **Activity dependent**

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

• Lasting changes produced in active system
  Reato, *J Neurophys.* 2014
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