tDCS: Introduction and General Principles

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Soterix Medical Inc. produces tDCS and High-Definition tDCS. Marom Bikson is founder and has shares in Soterix Medical.

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Transcranial Direct Current Stimulation (tDCS)

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

What are the mechanisms of tDCS that allow for specificity?
tDCS electrode position on the head determines which regions are stimulated

- Current flows from one electrode to the other

Truong et al. Clinician accessible tools for GUI computational models. “BONSAI” and “SPHERES”. *Brain Stimulation* 2014
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)
tDCS: Direct Current stimulation of columns

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: tDGS

How does Direct Current change cortical processing?
Brain Slice models of Direct Current Stimulation

All experimental data from acute brain slice of rat cortex of hippocampus - column scale

- No background activity, any synaptic input controlled in a pathway specific manner
- Voltage sensitive dye imaging
- Intracellular recording of identified cells / synapse
- Allows characterization of how Direct Current stimulation changes processing (input to output) by columns
Direct Current stimulation of columns: tDCS

How does Direct Current change cortical processing?
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

How does Direct Current change neurons?
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?

Brain slice: Optical Mapping with Voltage Sensitive Dyes

How does Direct Current change neurons?

Brain slice: Optical Mapping with Voltage Sensitive Dyes

How does Direct Current change neurons?

Intracellular recording and morphology

Layer II/III Pyramidal

Layer I Interneuron

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?

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

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

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Direct Current stimulation of columns: tDCS

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Direct Current stimulation of columns: tDCS

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

Pyramidal Neuron

No Direct Current

Anodal Direct Current

Cathodal Direct Current

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

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?

Pyramidal Neuron

Input

Direct Current

Output

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

How does Direct Current change synaptic efficacy?
Weak polarization modulates synaptic efficacy
Weak polarization modulates synaptic efficacy

- DC stimulation produces sustained polarization
- On-going synaptic activity boosted: plasticity
Weak polarization modulates synaptic efficacy

- Ongoing synaptic activity modulated while tDSCS sustained
- Substrate for plasticity
- Modulation of ongoing activity, *not* generation

Excitatory post-synaptic currents (field) in brain slice

Train of synaptic ongoing activity
Biophysical basis of tDCS functional selectivity

Fritsch 2010: BDNF dependent + activity dependent induction

Specific ongoing synaptic activity (no plasticity)

tDCS induces plasticity

“None-active” synapse

No tDCS synaptic plasticity

Synaptic Plasticity in brain slice
Biophysical basis of tDCS functional selectivity

Fritsch 2010: BDNF dependent + activity dependent induction
Specific ongoing synaptic activity (no plasticity)
tDCS induces plasticity

Kronberg 2015 + Rahman 2015: 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

- DC shifts plasticity (LTP/LTD) toward potentiation
- Dendrite depolarization boosts dendrite inputs (when soma is hyperpolarized)
• Inputs to dendrites depolarized by DCS are boosted (independent of soma polarization)
Biophysical basis of tDCS functional selectivity

- (Modulation of) plasticity is NMDA-R dependent
- No induction of plasticity in the absence of endogenous plasticity

Nitsche et al. Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. J. Physiol. 553, 293–301
Biophysical basis of tDCS functional selectivity
Biophysical basis of tDCS functional selectivity

- Modulation of theta-burst plasticity consistent with soma polarization
- Pathway specific (activity targeted modulation)

Theta-burst session no DCS

Theta-burst session with DCS
Biophysical basis of tDCS functional selectivity

- Modulation of theta-burst plasticity consistent with soma polarization
- Pathway specific (activity targeted modulation)
- DCS accelerates plasticity and increases maximum achievable gain

![Graph showing synaptic strength over time with and without DCS during theta-burst sessions.](image)
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

- Direct Current boosts ongoing plasticity,
  *process specific
  *leverages well established mechanisms
  Kronberg 2015
  Rahman 2015