Making tDCS effective and specific: insights from computational and animals 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.
The “sliding scale” explanation for tDCS (and brain function)

Brain function and disease as a change in regional “excitability”

As explained by:
- fMRI
- Lesion studies
- Drugs
- TMS...

Implies monolithic function of each brain region
Implies individuals vary in baseline or max “excitability”

tDCS as a universal modulator of regional brain “excitability”

“Cathodal” stimulation
- “Less” function, less neuronal activity
- “Less” excitatory plasticity (inhibition)

“Anodal” stimulation
+ “More” function, neuronal activity
“More” excitatory plasticity (excitatory)
Computational models predict brain current flow

- Two pad electrodes placed on head and connected to DC current stimulator.
- Current passed between ANODE(+) and CATHODE(-)
- DC CURRENT FLOW across cortex.
- Current is INWARD under ANODE and OUTWARD under CATHODE
Computational Modeling Studies on tDCS (neuralengr.com)


B. Kuo, Nitsche et al. Comparing cortical plasticity induced by conventional and high-definition 4x1 ring tDCS: a neurophysiological study. *Brain Stimulation*. 2013 6(4):644-8


Conventional and High-Definition Electrodes

Conventional bipolar large electrodes

High-Definition electrodes in “4x1” configuration

Datta et. al. Brain Stim 2009
Targeted High-Definition tDCS

- 5 small “HD” electrodes (4+1)
- 1 Center electrode over target determines polarity (anode, cathode)
- 4 return electrodes - Ring radius determines modulation area

Center electrode: CATHODE
Center electrode: ANODE

Outward current direction (inhibitory)
Outward current direction (excitatory)

Datta et. al. Brain Stim 2009
The focality of tDCS can be increased using “High-Definition” electrode arrays. Models can be used to design therapies such as 4x1 HD-tDCS.

Datta et al. *Brain Stim* 2009

But: The dose of conventional pad tDCS still determines brain current flow at the global and gyri-specific level.

Truong, Bestmann, Nitche
Neuromodulation with diffuse vs. focused tDCS

10 minutes of 2 mA 4x1 HD-tDCS produces >2 hour of after-effects

Kuo et. al. Brain Stim 2013
Neuromodulation with diffuse vs. focused tDCS

Conventional tDCS (2 mA)

High-Definition tDCS (2 mA)

B Kuo et. al. Brain Stim 2013

Red=inward
The focality of tDCS can be increased using “High-Definition” electrode arrays. Models can be used to design therapies such as 4x1 HD-tDCS.  
Datta et al. *Brain Stim* 2009

Focal HD-tDCS produces distinct neuromodulation then conventional pad tDCS.  
Kuo et al. *Brain Stim* 2013

But: 4x1 HD-tDCS optimization, validation + clinical trials are ongoing.

Caparelli-Daquer, Wassermann IEEE 2012 (TMS MEP)  
Borckardt, George et al. J. Pain 2012 (Experimental Pain)  
Dmochowski, Parra et al. Neural Engr. 2011 (Optimization)  
Villamar, Fregni et al Journal of Pain 2012 (Fibromyalgia)  
Dmochowski, Fridriksson, Parra et al. Neuroimage (Stoke)  
Edwards, Cortes et al. In Prep (Stroke)  
Fregni et al. In Prep (Fibromyalgia with biomarkers)  
Rothwell et al. In Prep (TMS MEP, focality)  
....
Validating 4x1 High-Definition tDCS

Transcranial Electrical Stimulation (TES) – short high-intensity pulse that triggers motor response (MEP)

(?!) Comparable focality to TMS

Edwards et. al. Neuroimage 2013
Validating 4x1 High-Definition tDCS

Subject specific modeling and experiments
Inter-subject variation in susceptibility >2x

- Change TES intensity to give same MEP response (left)
- Same TES intensity giving different MEP responses (right)
Computational Models of Transcranial Direct Current Stimulation

**A**
The focality of tDCS can be increased using “High-Definition” electrode arrays. Models can be used to design therapies such as 4x1 HD-tDCS.

_Datta et al. Brain Stim 2009_

**B**
Focal HD-tDCS produces distinct neuromodulation then conventional pad tDCS.

_Kuo et al. Brain Stim 2013_

**C**
Validation: HD-tDCS produces focal current flow. Anatomical variability is important for tDCS (as for TMS) and can be controlled with computational models.

_Edwards et al. Neuroimage 2013_
Individual variability of tDCS: anatomy

- Evaluated range of conventional and HD tDCS montages
- Male/female, super-obese/low-BMI...
- Considered magnitude of peak current in brain
- Location of peak current inside brain
- Maximum stimulator voltage (safety)
- Current density at scalp (sensation)

Truong et. al. Neuroimage Clinical 2013
The focality of tDCS can be increased using “High-Definition” electrode arrays. Models can be used to design therapies such as 4x1 HD-tDCS.  

Datta et al. Brain Stim 2009

Focal HD-tDCS produces distinct neuromodulation then conventional pad tDCS.

Kuo et al. Brain Stim 2013

Validation: HD-tDCS produces focal current flow. Anatomical variability is important for tDCS (as for TMS) and can be controlled with computational models.

Edwards et al. Neuroimage 2013

Anatomical variability can change magnitude and location of peak current. 4x1 HD-tDCS magnitude more sensitive, location is robust across individuals.

Truong Neuroimage Clinical 2013
Mechanisms and rational design of tDCS

Clinical trials, cognitive neuroscience, neurophysiology, imaging

Animal DCS

Tissue / brain slice DCS
Animal Brain Slice Studies on tDCS (neuralengr.com)


Transcranial Direct Current Stimulation (tDCS)

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MRI derived computational model
Explaining the mechanisms of tDCS (and rational tDCS optimization) requires linking brain current flow with changes in excitability.
Decreased Excitability / Plasticity

Increased Excitability / Plasticity

Origins of excitability changes under DCS

Animal studies 1950-1970 (Bindeman, Purpura, Creutzfeldt, Gartside)

With intensities 100x tDCS, polarity specific* changes in firing rate that outlast >5 minute stimulation

Clinical Neurophysiology (Nitsche, Paulus)
Polarity specific* changes in motor response to TMS that outlast >5 minute stimulation

Clinical trials: Changes in behavior
Conventional tDCS stimulation >50% of brain, not consistent

Imaging etc. Not conclusive despite overriding hypothesis

Depth: 1.1 mm (PT-cell)
Theory of neuron polarization by tDCS.
Theory of neuron polarization by tDCS

Current flow
outward    inward

Electrode
Head Surface
Cortical Neuron
Current flow
inward
outward

Head Surface

Anode (+)

Hyperpolarized cell compartments

Depolarized cell compartments

? Increased Excitability / Plasticity
Theory of neuron polarization by tDCS

Current flow

outward
inward

Head Surface

Cathode (-)

Depolarized cell compartments

Hyper-polarized cell compartments

? Decreased Excitability / Plasticity
Modulation of “excitability” under DCS

- Depolarized soma
  - Increased Excitability / Plasticity

- Hyperpolarized soma
  - Decreased Excitability / Plasticity

Current flow: outward to inward
Hippocampal Pyramidal Neuron Polarization under DCS

Optical Mapping with voltage sensitive dyes

Multi-compartment neuronal modelling

DC current flow

Bikson et. al. J. Physiol 2004
Direct current always produce bimodal polarization. e.g. Anodal stimulation produce soma depolarization and apical dendrite hyperpolarization.

Bikson J Physiol 2004
Cortical Pyramidal Neuron Polarization under DCS

Intracellular recording + Morphological reconstruction

Layer II/III Pyramidal

Layer I Interneuron

Layer V/VI Bursting Pyramidal

0.3 mV polarization per 1 V/m electric field

0.1 mV polarization per 1 V/m electric field

0 mV polarization per 1 V/m electric field

DC Current Flow

Radman et. al. Brain Stimulation 2009
Modulation of “excitability” under DCS

Current flow in/outward

Depolarized soma

Increased Excitability / Plasticity

Electric Field max: 0.4 V/m at 2 mA

0.4 V/m * 0.3 polarization per V/m =

Somatic polarization max: 0.12 mV

Hyperpolarized soma

Decreased Excitability / Plasticity

Radman et. al. Brain Stimulation 2009
Cellular Mechanisms of Transcranial Direct Current Stimulation

1. Direct current always produce bimodal polarization. e.g. Anodal stimulation produce soma depolarization and apical dendrite hyperpolarization. 
   Bikson J Physiol 2004

2. Under tDCS maximum somatic polarization is (only) 0.12 mV “Sub-threshold” “Neuromodulation” 
   Radman Brain Stim 2009
Modulation of “excitability” under DCS

Bi-modal polarization
Somatic polarization max: 0.12 mV

Radman et. al. Brain Stimulation 2009
Origins of excitability changes under DCS

- **Animal studies 1950-1970** (Bindeman, Purpura, Creutzfeldt, Gartside)
  - With intensities 100x tDCS, polarity specific* changes in firing rate that outlast >5 minute stimulation

- **Clinical Neurophysiology** (*Nitsche, Paulus*)
  - Polarity specific* changes in motor response to TMS that outlast >5 minute stimulation

- **Clinical trials: Changes in behavior**
  - Conventional tDCS stimulation >50% of brain, not consistent

- **Imaging etc..**
  - Not conclusive despite overriding hypothesis
Modulation of sensitivity to synaptic input under DCS

Anodal stimulation + evoked response

Cathodal stimulation (soma Hyperpolarized)

Control

Anodal stimulation (soma Depolarized)

fEPSP: metric of cellular synaptic efficacy

Rahman et al. J Physiol 2013

Current flow

Hyperpolarized dendrites

Depolarized soma

Layer V/VI

Synaptic efficacy

+ -
Modulation of sustainable synaptic processing

Higher sustained synaptic inputs under anodal stimulation
Modulation of “excitability” under tDCS

Current flow
outward  inward

Depolarized soma
Synaptic processing enhanced

Hyperpolarized soma
Synaptic processing inhibited

Rahman et. al. J Physiol 2013
Cellular Mechanisms of Transcranial Direct Current Stimulation

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Radman Brain Stim 2009

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Bikson J Physiol 2004

3. Synaptic efficacy is modulated with somatic polarization. e.g. Anodal stimulation enhances synaptic processing

Rahman J Physiol 2013
Direct Current Stimulation of Network Oscillations

Network Gamma Activity

Brain Slice

Network Model

Excitatory neuron / inhibitory neuron network

Adaptation
Stimulation

Anode DCS
Cathode DCS

Cathode DCS
Oscillation Power
Anode DCS

Reato et al J Neurosci 2010
Direct Current Stimulation of Network Oscillations

Network Gamma Activity

Excitatory neuron / inhibitory neuron network

- Feed-back excitatory/inhibitory synaptic loop enhances sensitivity to DCS
- DCS modulates dynamics of feed-back loop (independent of power)

Decreased excitatory synaptic function
Decreased inhibitory synaptic function

Increased excitatory synaptic function
Increase inhibitory synaptic function

Cathode DCS

Anode DCS

Oscillation Power

Reato et al J Neurosci 2010
Modulation of “excitability” under tDCS

Current flow

outward

inward

Depolarized soma

Hyperpolarized soma

Oscillation Power and Dynamics Enhanced

Oscillation Power and Dynamics Inhibited

Reato et al J Neurosci 2010
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   Bikson J Physiol 2004

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   Radman Brain Stim 2009

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   Rahman J Physiol 2013

4. DCS modulates power of ongoing network activity (oscillations). Underlying synaptic dynamics both determine sensitivity and are altered.

   Reato J Neurosci 2010
Alternating Current Stimulation of Network Oscillations

Network Gamma Activity

- AC stimulation
- Brain oscillations

Entrainment

Modulation

Reato et al., 2010

10 V/m

Increasing AC amplitude

0.2 V/m

Increasing AC frequency

Gamma peak (25Hz)

Double gamma peak (50Hz)

- Entrainment
- Frequency increased
- Subharmonics
- Frequency decreased
- Power modulation
- Spiking resonance
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Information processing altered by tDCS

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Implies monolithic function of each brain region
Implies individuals vary in baseline or max “exciability”

**tDCS modulate information processing capacity**

“Cathodal” stimulation

- Altered capacity and plasticity

“Anodal” stimulation

- More capacity for processing input and plasticity
  - Firing rate may not be changed
Brain function and disease modeled by how information is processed

Plasticity (learning) is a change in response to specific input rather than global change in “excitability”
Potential to train to specific inputs

Information processing altered by tDCS

“Cathodal” stimulation
Altered capacity and plasticity

“Anodal” stimulation
More capacity for processing input and plasticity
Firing rate may not be changed
tDCS mechanisms: Neuromodulation

Low-intensity DC + specific network activation
tDCS mechanisms: Neuromodulation

Low-intensity DC + specific network activation

Current flow across entire region
tDCS mechanisms: Neuromodulation

Low-intensity DC + specific network activation

Current flow across entire region

Modulation (plasticity) of only co-activated neurons
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