Design and optimization of tDCS for clinical trials: perspective from animal and computational studies

Marom Bikson, Ph.D.
The City College of New York

Lucas Parra, Asif Rahman, Niranjan Khadka, Dennis Truong, Belen Lafon, Gregory Kronberg, Ole Seibt
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 (tDCS)
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?

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, Sleep (SW, Lucid dreaming, Threat detection, Impulsivity, Compassion, Jealousy, Reality Filtering, IQ, Prejudice...
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.

How can a 9V battery affect the complex brain?
How is specificity of action achieved?

tDCS Publications
Depression, pain, migraine, epilepsy, PTSD, schizophrenia, autism, neglect, rehabilitation (motor, aphasia), TBI, OCD, 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.

High-Definition tDCS uses arrays of electrodes to focus current to targets.

Software allows you to generate subject and target specific (HD) tDCS “formulation”.

The math of targeting is “solved”

- Collateral targets
- Cost ($)
- Complexity of set-up
- Safety limits (historical)
- Regulatory constraints (regional)
- Anatomical specificity vs. “casting a wide net”
- .....

What target?
At what cost?
“4x1” montage of High-Definition tDCS

✓ Allows targeting of selected cortical regions

Datta et al. Gyri-precise model of tDCS: Improved spatial focality using a ring versus conventional pad. *Brain Stimulation* 2009
“4x1” montage of High-Definition tDCS

✓ Total of 5 small “HD” electrodes (4+1)
✓ Center electrode over target determines polarity 4 return electrodes - Ring radius determines modulation area
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
Where is the DLFPC?

Seibt al. The pursuit of DLPFC. *Brain Stimulation* 2015
One target, so many montages to try

Seibt, Rajji al. Montage for bilateral DLPFC. *In preparation*
One target, so many montages to try

MNI (special)

S# (tDCS standard)

Others (M/F, head size, age...)

Significant gross anatomy differences and cortical architecture

Seibt, Rajji al. Montage for bilateral DLPFC. *In preparation*
One target, so many montages to try

- Putting electrodes across the head produces current flow across the head
- Cortical folding negates any notion of global polarity specificity
- Local (DLPFC) polarity specific and current intensity optimization possible

Seibt, Rajji al. Montage for bilateral DLPFC. In preparation
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, Sleep (SW, Lucid dreaming, Threat detection, Impulsivity, Compassion, Jealousy, Reality Filtering, IQ, Prejudice…

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 (tDSCS) 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

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

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
- Polarize neurons
- Neuro-modulation: Interacting with specific ongoing neuron activity

tDCS
Biophysical basis of tDCS functional selectivity

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
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
tDCS: Sustained weak polarization

Intracellular recording and morphology

0.3 mV polarization

Layer I Interneuron

0 mV polarization

Layer II/III Pyramidal

0.1 mV polarization

Layer V/VI Bursting Pyramidal

0.3 mV polarization

Direct Current

1 V/m Direct Current

Radman, Bikson et al. Role of cortical morphology in uniform electric field stimulation. *Brain Stimulation* 2009
tDCS: Sustained weak polarization

Which compartments are polarized by DCS?

Soma < 0.3 mV

Dendrites

Axon (terminals) < 1 mV

1 V/m Direct Current

tDCS: Sustained weak polarization

Which compartments are polarized by DCS?

Afferent terminals

There are a lot of terminals and they point every which way

Biophysical basis of tDCS functional selectivity

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

Direct Current

Train of synaptic ongoing activity

Excitatory post-synaptic currents (field) in brain slice

- Ongoing synaptic activity modulated while tDCS sustained
- Substrate for plasticity
- Modulation of ongoing activity, *not* generation
Weak polarization modulates synaptic efficacy

- Polarity of modulation depends on many factors

Which compartments are polarized by DCS?
Which compartments are polarized by DCS?
Biophysical basis of tDCS functional selectivity

Fritsch 2010: BDNF dependent + activity dependent induction

Specific ongoing synaptic activity (no plasticity)

Ongoing Plasticity

Rahman 2015: Pathways specific + plasticity dependent modulation

“None-active” synapse

No tDCS synaptic plasticity

DC + Theta burst synaptic activity

Synaptic Plasticity in brain slice