State-of-the-art tDCS Protocols, Techniques, and Optimization

Getting “what we want” from neuromodulation

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Transcranial Direct Current Stimulation (tDCS)

- Non-invasive, portable, well-tolerated neuromodulation.
- Low-intensity (~2 mA) current passed between scalp electrodes (~20 min).
- Investigated for cognitive neuroscience and neuropsychiatric treatment.

Depression, pain, migraine, epilepsy, PTSD, schizophrenia, tinnitus, neglect, rehabilitation (motor, aphasia), TBI, OCD, attention, Accelerated learning (reading, motor skills, math, threat detection), memory...

- Can a “simple” intervention modulate brain function?
- How is specificity of action achieved? – How to get what we want?
The basic idea: 1) tDCS produces current flow in the brain that 2) polarizes neurons and synapses, 3) changing excitability

- 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 at ANODE and OUTWARD at CATHODE

Brain targeting software
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What makes tDCS specific?

With diversity of tDCS applications (neuropsychiatric treatment, rehabilitation, and learning): How do we get what we want ???

• **Anatomical targeting (specificity)**
The control of tDCS electrode placement to produce current flow in desired brain regions.

• **Functional targeting (specificity)**
The use of tDCS *adjunct* to behavioral / cognitive training to facilitate the outcomes of training.
Anatomical targeting with tDCS

- “Conventional” tDCS varies the position of two large electrodes.
- Montage specific effects on behavior and neurophysiology well documented.
- “Shaping” outcomes vs “targeting” brain regions.

Conventional bipolar large electrodes
Anatomical targeting with tDCS

High-Definition electrodes in “4x1” configuration

Conventional bipolar large electrodes

Datta et. al. Brain Stim 2009
Anatomical targeting with tDCS

Datta et. al. Brain Stim 2009

High-Definition electrodes in “4x1” configuration

Dmochowski Neural Engr. 2011

Optimized tDCS is a “closed” problem

But “best” montage different for:

a) Maximum **intensity** at target.

b) **Focality** (minimizing relative intensity outside of target).
Customized targeting with tDCS

Super-obese
Obesity / Craving / Addiction

Truong Neuroimage 2013

Stroke
Rehabilitation (motor, aphasia)

Datta Brain Stimulation 2011
Dmochowski Neuroimage 2013

Pediatric
Epilepsy / ADHD / CP

Kessler PLoS ONE 2013
Gillick Frontiers 2014
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- Conventional (pad) tDCS montage shapes current flow and neurophysiologic/behavioral outcomes.
- High-Definition tDCS enhances causal testing of regional function and leads to distinct outcomes.
- “Rule-of-thumb” montage design enhanced with models.
- Inter-individual anatomical differences can be accounted for including in aging/TBI/stroke/children/obesity...
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tDCS mechanisms: Neuromodulation

High-intensity Pulses

Over-driving a neural network

Neuromodulation comes from secondary non-linear changes

Low-intensity DC

Deep Brain Stimulation
Motor Cortex Stimulation
Transcranial Magnetic Stimulation (TMS)
tDCS mechanisms: Neuromodulation

High-intensity Pulses

Over-driving a neural network

Low-intensity DC
tDSC mechanisms: Neuromodulation

High-intensity Pulses

Over-driving a neural network

Low-intensity DC
tDCS mechanisms: Neuromodulation

High-intensity Pulses

Over-driving a neural network

Low-intensity DC

Interacting with specific activity in a neural network (Neuromodulation)
From Anatomical Targeting to Functional Targeting

Network of interest (e.g. depression, math cells)

Other networks – not targets for neuromodulation

Electrode / Coil

Preferential modulation of more active network (activity dependent)

Current flow across entire region

Network of interest (e.g. depression, math cells)
**Synaptic Efficacy: evoked activity**

Direct Current stimulation + evoked response

- **fEPSP:** metric of cellular synaptic efficacy
  - Bikson et al. 2004, Rahman et al. 2013

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

**Modulation**

- **Synaptic efficacy**

- **Hyperpolarized dendrites**
- **Depolarized soma**
- **Layer V/VI**
Biophysical basis of tDCS functional selectivity

• Higher sustained synaptic inputs under anodal stimulation
• Substrate for plasticity + Pathway specific
Synaptic Plasticity

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

- **Ranieri 2012**: Adaptive response (DCS then LTP) + Additive neuromodulation (of ongoing LTP)
  - Ongoing Plasticity
  - tDCS modulates plasticity

“None-active” synapse

No tDCS synaptic plasticity
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• **Functional targeting (specificity)**
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• **Direct Current Stimulation (DCS)** of silent network does not produce firing or changes in plasticity.
  • DCS modules synaptic efficacy.
  • DCS can modulate network activity not producing plasticity to produce plasticity.
  • DCS can modulates network activity producing more plasticity.
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Rational tDCS Clinical Trials: Specificity

- Phase-2 Harvard/Spaulding (Fregni, Geva): Fibromyalgia ongoing
- End-point 50% reduction in pain: Adaptive therapy
- Soterix Medical HD-tDCS
- thermode (pain evoked potential) -> Elminda EEG
- Principle of both anatomical and functional targeting
- End-point met in >%50
  - All electrographic responders
- Data-base (“cloud”) on brain response
  - Informs future treatment
- Molecular (u-opiod) imaging (DaSilva)

Can a “simple” intervention modulate brain function?
How is specificity of action achieved? – How to get what we want?
tDCS montages for treatment of Depression

- Brunoni et al.
  SELECT / ELECT
  Anode DPLPC
  2.0 mA
  Double blind RCT

- Loo et al.
  Multi-Center Trial
  Anode DPLPC
  2.5 mA
  Double blind RCT
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Slides (PDF) and selected references supporting conclusions at: Neuralengr.com
Extra Slides
References on Computational Modeling Studies on tDCS / HD-tDCS for anatomical targeting


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


References on Animal Studies on Functional Targeting


Neuromodulation: Electrotherapy Delivery Platforms

- Deep Brain Stimulation (invasive)
- Transcranial Magnetic Stimulation
- Transcranial Direct Current Stimulation

**Decreasing Cost**
- Deployable, compact
- Minimal supervision
- Adverse events: itching, erythema
- IRB / FDA “NSR”

**Decreasing Risk**

**Increasing Efficacy, Specificity**

- tDCS Specificity
Anatomical targeting with brain stimulation

Supra-threshold stimulation

DBS
Cortical stim
TMS

Sub-threshold stimulation

HD-tDCS
4x1


Stimulation primary neuromodulation target. Endogenous circuit.
tDCS neuromodulation (conditioning): The Basic Finding

Kuo et. al. Brain Stim 2013

- After tDCS excitability is modulated. Anode=UP, Cathode=DOWN.
- Clinical trials “rationalized” based on shifting excitability
tDCS dose: Waveform

Intensity (mA), Duration (minutes)

- Anode (1 mA, 20 min) - 30 min
- Cathode (-1 mA, 20 min) - 30 min

Outcome (behavior)

Linear dose-response

Repetition

Current intensity

Time

Intensity
tDCS dose: Waveform

Intensity (mA), Duration (minutes)  Ramp (e.g. LTE), repetition...

- Anode (1 mA, 20 min) 30 min
- Cathode (-1 mA, 20 min) 30 min

Non-linear dose-response (none-monotonic)
And
Brain-state dependent
Direct Current Stimulation of Network Oscillations

Network Gamma Activity

Cathode DCS (-6 V/m)

Anode DCS (6 V/m)

Brain Slice + Computational Model
Reato J. Neurosci 2010
Direct Current Stimulation of Network Oscillations

- **Boost (anode) or suppress (cathode) ongoing gamma oscillations**

- **Direct Current** does not “produce” oscillations, but modulates ongoing activity.

**Brain Slice + Computational Model**
Reato J. Neurosci 2010
Deployable tDCS (keeping is simple)

- Repeated sessions (e.g. weeks) required for efficacy and maintenance.
- Home-based therapy reduces burden on patients (travel) and hospital (cost).
- “Home” technology focused on compliance.