Principles and Modeling of Transcranial Direct Current Stimulation

Getting “what we want” from neuromodulation

Dec 4, 2014
Clinical, Assessments and Intervention Updates in Neurorehabilitation Course
Harvard Medical School / Spaulding

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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.
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?
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
The basic idea: tDCS produces current flow in the brain with polarizes neurons

- 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
The basic idea: tDCS produces current flow in the brain with polarizes neurons
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Current flow

outward

inward

Anode (+)

Head Surface

Hyperpolarized cell compartments

Depolarized cell compartments

Increased Excitability / Plasticity
The basic idea: tDCS produces current flow in the brain with polarizes neurons.

- Current flow: inward/outward
- Cathode (-) / Head Surface
- Current Flow
- Depolarized cell compartments
- Hyper-polarized cell compartments
- Decreased Excitability / Plasticity
tDCS neuromodulation: 1 slide on the Basic Finding and clinical rationale

Kuo et. al. Brain Stim 2013

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

![Diagram showing tDCS modulation of TMS motor evoked potentials]

**Cathodal stimulation** (soma Hyperpolarized)

**Brain “Excitability”**

**Anodal stimulation** (soma Depolarized)

**Modulation**
Modulation of “excitability” under DCS

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

Brain “Excitability”

Increased Excitability

Decreased Excitability

Cognitive, behavioral, clinical benefit

Current flow
outward
inward

Modulation

-
tDCS dose: Waveform

Intensity (mA), Duration (minutes)

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

Outcome (behavior)

Intensity

Linear dose-response

Repetition
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

Current intensity

Time

Outcome (behavior)

Non-linear dose-response (none-monotonic)
And
Brain-state dependent
What makes tDCS specific?

Given the diversity of tDCS application spanning neuropsychiatric treatment, rehabilitation, and learning in healthy individuals.

- **Anatomical targeting (specificity)**
  The control of tDCS Dose (Peterchev Brain Stim 2013) electrode placement to produce current flow in targeted brain regions.
  Design facilitated by current flow models.

- **Functional targeting (specificity)**
  The use of tDCS *adjunct* to behavioral / cognitive training to facilitate the outcomes of training.
  Design facilitated by quantitative descriptions (cellular models) developed using animal experiments.
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.
Anatomical targeting with tDCS

High-Definition electrodes in “4x1” configuration

Conventional bipolar large electrodes

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

High-Definition electrodes in “4x1” configuration

Datta et. al. Brain Stim 2009

Optimized tDCS is a “closed” problem
But “best” montage different for:
  a) Maximum **intensity** at target.
  b) **Focality** (minimizing relative intensity outside of target).

Dmochowski Neural Engr. 2011
Customized targeting with tDCS

Super-obese
Obesity / Craving / Addiction

Pediatric
Epilepsy / ADHD / CP

Stroke
Rehabilitation
(motor, aphasia)

Truong Neuroimage 2013

Datta Brain Stimulation 2011
Dmochowski Neuroimage 2013

Kessler PLoS ONE 2013
Gillick Frontiers 2014
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.

- **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...
tDCS mechanisms: Neuromodulation

**High-intensity Pulses**

Over-driving a neural network

Neuromodulation comes from secondary non-linear changes

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**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
tDCS mechanisms: Neuromodulation

High-intensity Pulses

Low-intensity DC

Over-driving a neural network
tDCS mechanisms: Neuromodulation

High-intensity Pulses

Over-driving a neural network

Low-intensity DC

Interacting with specific activity in a neural network (Neuromodulation)
Anatomical targeting with brain stimulation

**Supra-threshold stimulation**
- DBS
- Cortical stim
- TMS


**Sub-threshold stimulation**
- HD-tDCS
- 4x1

Stimulation primary neuromodulation target. Endogenous circuit.
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
What makes tDCS specific?

“Given” the diversity of tDCS application spanning neuropsychiatric treatment, rehabilitation, and learning in healthy individuals:

- **Anatomical targeting (specificity)**
  The control of tDCS Dose (Peterchev Brain Stim 2013) through coil / electrode placement to produce current flow in targeted brain regions.
  Design facilitated by current flow models.

- **Functional targeting (specificity)**
  The use of tDCS *adjunct* to behavioral / cognitive training to facilitate the outcomes of training.
  Design facilitated by quantitative descriptions (cellular models) developed using animal experiments.
Biophysical basis of tDCS functional selectivity

Synaptic Efficacy: evoked activity

Direct Current stimulation + evoked response

fEPSP: metric of cellular synaptic efficacy

Cathodal stimulation
(soma Hyperpolarized)
Control
Anodal stimulation
(soma Depolarized)
• 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

? Molecular substrate   ? Role of timing (dose)
What makes tDCS specific?

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

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

• 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 plasticity to produce more plasticity.
Rational tDCS Clinical Trials: Specificity

• Phase-2 Harvard/Spaulding (Fregni, Geva): **Fibromyalgia ongoing**
• End-point 50% reduction in pain: **Adaptive therapy**
• **HD-tDCS**
• **thermode** (pain evoked potential) -> 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?
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 with references up now at neuralengr.com
Further 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


Check [http://bme.ccny.cuny.edu/people/faculty/mbikson](http://bme.ccny.cuny.edu/people/faculty/mbikson) for complete PDFs
Further References on Animal Studies on Functional Targeting


Check [http://bme.ccny.cuny.edu/people/faculty/mbikson](http://bme.ccny.cuny.edu/people/faculty/mbikson) for complete PDFs
Direct Current Stimulation of Network Oscillations

Network Gamma Activity

Anode DCS (6 V/m)

Cathode DCS (-6V/m)

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

Network Gamma Activity

- 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
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)

Current intensity

Time

Repetition

… … … … … …

Outcome (behavior)

Linear dose-response

Intensity

-2 mA

2 mA

Anode (1 mA, 20 min) 30 min)

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

Outcome (behavior)

- +

- +

- +

- +

...
tDCS dose: Waveform

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

Current intensity

Time

2 mA
Anode (1 mA, 20 min)  30 min

Cathode (-1 mA, 20 min)  30 min

Non-linear dose-response (none-monotonic)
And
Brain-state dependent

Outcome (behavior)

Intensity
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.
**High-Definition tDCS 4x1-Ring Montage**

*NeuroImage 2012*
Edwards D, Cortes M, Datta A, Minhas P, Wassermann EM, Bikson M

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

(F3) TES TMS

anterior

Primary Motor Cortex (C3)

posterior

(P3) TES TMS

(?) Comparable focality to TMS
High-Definition tDCS 4x1-Ring Montage

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)