Translational Research in transcranial Direct Current Stimulation (tDCS) for Seizures

Dec 6, 2014
AES Neurostimulation and Neuroengineering: New Directions

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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.
Translational Research on tDCS for seizures

- Animal studies of direct current stimulation for seizure control
- Transcranial Direct Current Stimulation (2000-)
- New technology: High-Definition tDCS (2010)
- New trials of seizure control in humans (2014-)
Direct Current produces inhibition through polarization

- Direct current stimulation produces tonic membrane polarization
- “Cathodal” stimulation produces somatic hyperpolarization

-1 mA applied to scalp produced -0.3 V/m at cortex

Computational models: Datta, Bikson, Brain Stimulation 2009

-1 V/m at cortex produces -0.3 mV somatic polarization

Brain slice: Radman, Bikson, Brain Stimulation 2009
Somatic hyperpolarization by Direct Current and seizures

Acute animal models

- Epileptiform activity (ionic imbalance, drugs)
- After-discharges (tetanic stimulation)

DC Stimulation

- Reduces ictal/inter-ictal frequency
- Increases threshold

Ongoing seizures not stopped

“Works” in every animal model of epilepsy

- Sufficient somatic hyperpolarization: any activity is suppressed
- Neurophysiological substrate (clearer than High Frequency Stim)

Durand, Bikson *Proceedings IEEE* 2001
Sunderam, *Epilepsy and Behavior* 2010

Why a dearth of epilepsy clinical trials with direct current?

1. Non-invasive direct current stimulation: Need 10 mA to produce 3 V/m, painful and hazardous
2. Invasive direct current stimulation: electrochemically unstable
Transcranial Direct Current Stimulation (tDCS)

- Non-invasive, portable, well-tolerated
- Low-intensity (~2 mA) current for ~20 min
- Produces polarity specific shift in neuronal excitability during and after stimulation
  Nitsche and Paulus, 2000
- Investigated for cognitive neuroscience and neuropsychiatric treatment
  (>500 ongoing clinical trials)

Results form early tDCS epilepsy trials: encouraging but mixed
1. Given non-significant-risk profile: use may be justified even with varied effects.
2. Technology is not optimized.
   - Low dose / refractory patients: pre-clinical sensitivity in EEG
   - Drug interactions are not controlled (expected to interact)
   - Current flow diffuse and biphasic (excitation under anode)
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

Datta et. al. Brain Stim 2009
• Cathodal 4x1 HD-tDCS applied at 1 mA for 20 min
• EEG accessed before, during, after HD-tDCS

• Clinical trial for HD-tDCS for focal epilepsy. Ongoing at Boston Children's (PI Rotenberg) and NYU (PI Liu)
• Funded by the Epilepsy Therapy Project and Wallace Coulter Foundation
• Epilepsia partialis continua
  ➢ Severity of epilepsy approximate animal models
  ➢ Conspicuous marker
  ➢ Target and montage well defined – superficial
High-Definition tDCS trial for status epilepsy

- Cathodal 4x1 HD-tDCS, 1 mA, 20 min
- EEG accessed before, during, after HD-tDCS
High-Definition tDCS trial for status epilepsy

- Cathodal 4x1 HD-tDCS, 1 mA, 20 min
- EEG accessed before, during, after HD-tDCS
NYU-P01

![Graph showing power spectral density (PSD) across frequency bands.](image)

**P4 Spectrogram PRE - POST**

- **Power decreasing**
- **Power increasing**

**Average Interictal Discharge Frequency**

- **20 min HD-tDCS**
Neuromodulation: Electrotherapy Delivery Platforms

- **Deep Brain Stimulation (invasive)**
  - Decreasing Cost
  - Decreasing Risk
  - Increasing Efficacy, Specificity

- **Transcranial Magnetic Stimulation**
  - HD-tDSC

- **Transcranial Direct Current Stimulation**
  - Deployable, compact
  - Minimal supervision
  - Adverse events: itching, erythema
  - IRB / FDA “NSR”
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
tDSCS 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)
Anatomical targeting with brain stimulation

Supra-threshold stimulation

DBS  Cortical stim  TMS


Sub-threshold stimulation

HD-tDCS  4x1

Stimulation primary neuromodulation target. Endogenous circuit.
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Extra Slides
tDCS neuromodulation: 1 slide on the Basic Finding and clinical rationale

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

Kuo et. al. Brain Stim 2013

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Cathodal stimulation (soma Hyperpolarized)  →  Brain “Excitability” →  Anodal stimulation (soma Depolarized)
High-Definition electrodes in “4x1” configuration

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

Datta et. al. Brain Stim 2009

Anatomical targeting with tDCS
Customized targeting with tDCS

Super-obese
Obesity / Craving / Addiction

Pediatric
Epilepsy / ADHD / CP

Stroke
Rehabilitation (motor, aphasia)

Kessler PLoS ONE 2013
Dmochowski Neuroimage 2013

Truong Neuroimage 2013

Gillick Frontiers 2014

Datta Brain Stimulation 2011
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...
High-Definition tDCS 4x1-Ring Montage

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

(?) 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)