Targeted tDCS for Epilepsy control

Marom Bikson

Support: NIH-NINDS, Epilepsy Foundation, Wallace H. Coulter Foundation

The City College of New York: Neuroengineering
Transcranial DC Stimulation (tDCS)

- An “old” technique re-discovered in 2000
- Low-intensity Direct Current (DC) passed between to scalp electrodes. **1-2 mA**
- tDCS is well tolerated in clinical trials (main adverse event: transient itching).
- Decades on animal research showing modulation of neuronal firing by Direct Current

**Functional Insights?**
- Modifications of cAMP (Hattori, 1990)
- Increase in protein kinase C and calcium levels (Gartside 1964, Islam 1995)
- Short term: resting membrane potential and synaptic efficacy (Bikson 2004) – instant
- Long term: LTP- and LTD-like phenomena (Nitsche and Paulus 2000) >10 minutes of stimulation
DC instantly modulates neuronal firing in a *direction-specific* manner

**Cathode**
- Reduces action potential rate
- Increases firing threshold
- Reduces responsiveness to synaptic input

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Polarity specificity of Direct Current (DC) modulation

**Anode**

**Cathode**

![Anode Diagram](image1)

![Cathode Diagram](image2)

*Purpura McMurry 1965*
tDCS mechanisms: Neuromodulation

High-intensity Pulses

Over-driving a neural network

Low-intensity Cathode DC

Any inhibitory action secondary to increased activity
tDCS mechanisms: Neuromodulation

High-intensity Pulses

Over-driving a neural network

Any inhibitory action secondary to increased activity

Low-intensity Cathode DC

Direct Inhibition
tDCS mechanisms: Neuromodulation

How cathode tDCS decreases excitability?

Under Cathode: Hyperpolarized soma = Decreased excitability/plasticity?

Under Anode: Depolarized soma = Increased excitability/plasticity?
Electrographic Seizure Control with Direct Current

Epilepsy = Recurrent Seizures

Excitability ↔ Action Potentials
Electrographic Seizure Control with Direct Current
Increasing excitability by “convulsant” treatment leads to TONIC seizure-like activity.

Can seizures be controlled by electrical stimulation that decreases excitability?
Electrographic Seizure Control with Direct Current

Ghai, Bikson, Durand. J Neurophys 2000
Electrographic Seizure Control with Direct Current

Minimum electric field required for suppression (mV/mm)

3.7 ± 1.8  
13.7 ± 2.9  
X
Pre-clinical data

PTZ injection, one-channel EEG, 0.1 mA / 1 mA, anode/cathode/sham

Decades of pre-clinical data, diverse *in vitro* and *in vivo* models. Across models cathode Direct Current (DC) stimulation:
- Acute: reduces severity
- Acute: Sufficient intensity suppress ongoing activity
- Variable results on post-stimulation effects (anti-epileptic, no changes)
**Summary of Decades of Experience**

- For cathode DC fields hyper-polarization pyramidal neuron soma.
- Small DC fields produce linear polarization with a sensitivity of ~0.3 mV polarization per V/m applied field.
- Time constant to maximum polarization: 15-60 ms
- Prolonged DC current (minutes) can produce lasting changes (plasticity).
- In every animal models tested, DC field can suppress electrographic seizures.
- May be impractical for chronic implant.
Inhibition with high-intensity AC fields?

Simple expectation:

- Field
- Intracellular

→ Increase in AP rate / increase in excitability
Inhibition with high-intensity AC fields?

Transcranial Magnetic Stimulation (TMS)

Deep Brain Stimulation (DBS)

Stimulation of a targeted structure mimics the effects of lesioning that structure

→ High frequency AC stimulation inhibits the targeted structure
Experimental Set-up
Induced (low-frequency) seizure-like activity

Applied 50 Hz sinusoidal fields

↓

Low-pass filter
Effects of AC Electric fields on Electrographic Seizures

Electrographic seizure control

Low Intensity (<50 mv/mm)

High Intensity (>100 mv/mm)

Bikson et al. J Physiol 2001
Effects of AC Electric fields on Electrographic Seizures

Extracellular/Intracellular Recording

Stimulation

Field

Transmembrane

10/20 mV
5 sec

20 mV
5 sec
Effects of AC Electric fields on Electrographic Seizures

Extracellular/Intracellular Recording

Stimulation

Field

Transmembrane

Transmembrane-Low-pass Filtered
Effects of AC Electric fields on Electrographic Seizures

**Extracellular/Intracellular Recording**

**Stimulation**

- **Field**
- **Transmembrane**

*Note: The diagrams illustrate the electrical activity before and during stimulation.*
Effects of AC Electric fields on Electrographic Seizures

Optical Mapping

Stim

50 Hz 1 mA

ΔF

600 m sec

[Images of optical mapping data]
Effects of AC Electric fields on Electrographic Seizures

$[K^+]_o$ recording
Effects of AC Electric fields on Electrographic Seizures

\[ [K^+]_o \text{ recording} \]

Low Intensity Stimulation

High Intensity Stimulation

1.5 mM K⁺

1 mV

30 sec

2 mM K⁺

1 mV
Use of sinusoidal fields allowed for recording during high frequency stimulation

Across animal models, during high frequency stimulation (high-intensity sinusoid or pulses) results in potassium efflux,

1. Tonic neuronal depolarization and suppresses action potential generation.

2. Tonic pacing of firing at stimulation frequency.

Possible relation clinical Deep Brain Stimulation for movement disorders. But what implication for behaviour outcomes in epilepsy?

Suppression was not orientation dependent.

POST-stimulus refractory period. Related to potassium re-
**Clinical data**

Transcranial direct current stimulation in refractory continuous spikes and waves during slow sleep: A controlled study

Edina T. Varga\(^{a,b}\), Daniella Terney\(^{a,b}\), Mary D. Atkins\(^{a}\), Marina Nikanorova\(^{c-g}\), Ditte S. Jeppesen\(^{d}\), Peter Uldall\(^{e}\), Helle Hjalgrim\(^{f,g}\), Sándor Beniczky\(^{a,h,*}\)

<table>
<thead>
<tr>
<th>Study Details</th>
<th>Outcomes</th>
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<tbody>
<tr>
<td>N=5, 1 session cathodal tDCS</td>
<td>did not reduce spike-index</td>
</tr>
<tr>
<td>N=1, 10 sessions</td>
<td>reduced seizure attacks from 8 to 6</td>
</tr>
<tr>
<td>N=2, 3 weekly sessions</td>
<td>reduced interictal epileptiform discharge</td>
</tr>
<tr>
<td>N=27, 1 session</td>
<td>reduced discharge frequency immediately, 24h and 48h after</td>
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Conventional tDCS used two large electrodes (anode, cathode)

- Diffuse current flow (collateral targets)
- Bi-directional excitability changes

Datta Bikson 2009

Cathode: inhibition
Anode: excitation

Datta Coslett 2010
Conventional tDSCS: Current flow

High-Definition tDSCS (HD-tDSCS) using arrays of smaller electrodes

- Focal current flow (targeted)

- Uni-directional excitability changes

Cathode 4x1 HD-tDSCS: Focal suppression with non-invasive electrical stimulation
High-Definition tDCS (HD-tDCS) in children

High-Definition tDCS (HD-tDCS) as a platform for epilepsy control
- Focal modulation of selected cortical target
- Cathodal (un-directional) modulation
- Integrated with EEG
- Robust across adult/pediatric head sizes
HD-tDCS Optimization

- Flexible montage with a single system (individualized)
- Automatic targeting software (physician GUI)

Dmochowski Datta Parra 2009
HD- tDCS Safety/Tolerability/Efficacy

- Experimental pain (2 mA/20 min) - George, Borckardt 2012
- TMS-MEP (1 mA/20 min) - Caparelli-Daquer 2012
- TMS-MEP (2 mA/10 min) - Nitsche 2013
- Direct Targeting Validation - Edwards 2012
- Stroke Rehabilitation (aphasia): Frederickson 2012
- Migraine Pain: DaSilva (ongoing)
- Stroke Rehabilitation (motor): Edwards (ongoing)
- Autism: Caparelli-Daquer (ongoing)
- Fibromyalgia Pain: Fregni 2013

- Compared to conventional tDCS, focal HD-tDCS High-magnitude, longer lasting effects, less sensation (tingling)
Focal status epilepticus (FSE) trial (ongoing)
PI: Alexander Rotenberg- Children’s Hospital Boston

- Phase-1: Safety and tolerability
- Emphasis on acute control (Cathode DC hyperpolarization*)
- Inclusion: Cortical focus
- 4x1 HD-tDCS: Anatomically restricted focal DC stimulation (safety)
- Cathodal inhibitory unidirectional stimulation (no collateral excitation)
- EEG integration*(Simple interference with EEG monitoring/ clinical management)
- Phase-2: Integrated stand-alone system*

HD-tDCS electrode integrated directly into EEG cap
Brain re-fibrillator

Cathode direct current hyperpolarizes soma
Targeted tDCS for Epilepsy control

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The City College of New York: Neuroengineering
Electric Field
Hyper-polarized cell compartments

Electric Field

Depolarized cell compartments
Electric Field

Hyper-polarized cell compartments

Depolarized cell compartments
Head Surface

ANODE

Hyper-polarized cell compartments

Electric Field

Depolarized cell compartments
(The only other thing you need to know about) **Sub-threshold polarization**

Soma Polarization = Electric Field * $G_{coupling}$

Electric Field

Soma Polarization

Soma polarization

Slope $\rightarrow G_{coupling}$

Electric Field
Head Surface

Hyper-polarized cell compartments

Depolarized cell compartments

Soma Polarization = Electric Field * $G_{coupling}$
How does DC sub-threshold electrotherapy work?

Can specific cell types be “targeted” by electrical stimulation?

Neuronal Morphology
How does DC sub-threshold electrotherapy work?

Can specific cell types be targeted by electrical stimulation?

**Neuronal Morphology**

- Depolarized cell compartments
- Hyper-polarized cell compartments

DC Uniform Field
How does DC sub-threshold electrotherapy work?

Can specific cell types be targeted by electrical stimulation?

**Neuronal Morphology**

Hyper-polarized cell compartments

$G_{coupling} = 0$

DC Uniform Field

Depolarized cell compartments

$G_{coupling} = $ Something
How does DC sub-threshold electrotherapy work?

Predictive Algorithms for Sub-threshold Morphological Sensitivity = $G_{coupling}$

Layer I Interneuron

Layer II/III Pyramidal

Layer V/VI Bursting Pyramidal

Dendrite Terminal Sensitivity

Somatic Sensitivity ($G_{coupling}$)

Action Potential Sensitivity (threshold)
How does DC sub-threshold electrotherapy work?