Behavioral Intervention Research using tDCS

What to think about?
What guesses do we make?
What do we know and what don’t we?
Disclosure

• Scientific Advisory Board Member for Neuronix, Nexstim, Neosync, Starlab, Neuroelectrics, Neurostim, Magstim, Axilium
• Serve on Device Expert Panel at FDA
• Funding from National Institutes of Health, National Science Foundation, Michael J Fox Foundation, Sidney-Baer Foundation, various other private Foundations
• I will talk about off-label applications of tCS
Rise in annual scientific publications

Source: www.clinicaltrials.gov 11/29/13
Autoimmune diseases
Visual diseases
Auditory diseases
Gastrointestinal issues
Demyelinating diseases
Diabetes
Epilepsy
Metabolic diseases
Menopause
Hydrocephalus
Necrosis
Pancreatitis
Poisoning
Postoperative complications
Pruritus
Respiratory disorders
Wounds and injuries
Rheumatic diseases
Scotoma
Skin diseases
Urinary diseases
Urologic diseases
Vascular diseases
Virual diseases
tCS in Behavioral Research

• Why do tCS?
• When do tCS?
• For how long to do tCS?
• How to do tCS?
  – How much?
  – With what electrode arrangements?
  – What electrode size?
Anodal or Cathodal tCS?

Cephalic Reference

Extra-Cephalic Reference
Anodal or Cathodal tCS?

Multiple "Exit" Electrodes

Nearly Monopolar Stimulation
Anodal or Cathodal tCS?

We have a nomenclature problem!!
Do not be fooled by it!!
What is tES dose?

Transcranial Electrical Stimulation (tES) dose is defined by all parameters of the stimulation device that affect the current flow generated in the brain:

1. **Electrode Montage**: number, shape, size, position.
2. **Waveform**: Current waveform parameters: pulse width, amplitude, polarity, repetition frequency; and interval between stimulation sessions and total number of sessions.

**tDCS**: Direct Current

**Nomenclature defined**: Guleyupoglu, Bikson et al. Classification of methods in transcranial electrical stimulation (tES). *J Neurosci Methods* 2013; 219(2) 287-311

**Dose defined**: Peterchev, Bikson et al. Fundamentals of transcranial electric and magnetic stimulation dose: Definition, selection, and reporting practices. *Brain Stimulation* 2012; (5) 435-53
tDCS dose: Waveform

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

Current intensity

Time

Outcome (behavior)

Linear dose-response

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

Intensity

DO NOT COPY
tDCS dose: Waveform

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

Current intensity

Time

Outcome (behavior)

Intensity

Non-linear dose-response (none-monotonic)
tDCS dose: Electrode montage

Number, position, and shape.

5x5 cm, M1 (anode), SO (cathode)

“Lateralized” Montage

Extra-cephalic Montage

Materials, High-Definition...
(!) Electrode design and preparation is the most important factor for consistent set-up, tolerability, and safety

- Pad fluid leak (e.g. pressure, view obstructed)
- Dry out (e.g. pad material, view obstructed)
- Pad re-use (contamination)
- Critical with High-Definition electrodes (but cannot be ignored with pads)
tDCS dose

Simple Goal: To increase excitability in cortex under the anode and decrease excitability under the cathode (ignore rest of brain)

(!) There is a biophysical basis for polarity specific excitability changes. But, this simple dose approach is NOT supported by engineering design (or much clinical testing)
Pharmacologic activity (efficacy and safety) is determined by drug concentration at tissue. Clinical dose is set by systemic application (tablets...).

Electrical activity (efficacy and safety) is determined by current flow at tissue. tDCS dose is set by surface application (stimulators and pads/coils). Computational models predict the current flow generated in the brain for a specific stimulation configuration/settings.
Computational models predict brain current flow

- 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
Evaluated range of conventional and HD tDCS montages

- Male/female, super-obese/low-BMI...
- Considered magnitude of peak current in brain
- Location of peak current inside brain
- Maximum stimulator voltage (safety)
- Current density at scalp (sensation)
M1-Supraorbital

Adolescent
8 year old
Scalp Potential
2 mA

Adolescent
12 year old
Scalp Potential
2 mA
1 mA

Adult
Scalp Potential
2 mA

Electric Field/Current Density
0 33% 66% >0.6 V/m
What do we know?

• Does not lead to neuronal firing
  – Purely modulatory
  – Combination with other interventions

• Does change firing rate likelihood of neuronal ensembles
  – Polarity dependent
  – Neuronal network impact
  – Shifts oscillatory brain activity

• Bipolar
  – Both anode and cathode have an effect
  – Entry and exit electrodes
  – Can be ‘almost monopolar’
Neurons? Which ones?

- Pyramidal Neurons?
- Glia?
- Axon hillocks?
- Dendritic branches?
Neurons? Which ones?
Theory of neuron polarization by tDCS

Current flow

outward  inward

DO NOT COPY
Theory of neuron polarization by tDCS

Current flow
outward  inward

Electrode

Head Surface

Cortical Neuron
Theory of neuron polarization by tDCS

Current flow
outward  inward

Anode (+)

Head Surface

Hyperpolarized cell compartments

Depolarized cell compartments

? Increased Excitability / Plasticity
Theory of neuron polarization by tDCS

Current flow

- Outward
- Inward

Head Surface

Cathode (-)

Current Flow

- Depolarized cell compartments
- Hyper-polarized cell compartments

Decreased Excitability / Plasticity
Modulation of “excitability” under DCS

Depolarized soma

Hyperpolarized soma

Increased Excitability / Plasticity

Decreased Excitability / Plasticity

Current flow
outward
inward
I. Molecular
II. External granular
III. External pyramidal
IV. Internal granular
V. Internal pyramidal
VI. Polymorphous
tDCS modifies MEP’s

Corticospinal Excitability

Test

Retest

EMG

Arm movement

Motor neuron to biceps muscle

Biceps muscle, contracting
Can tDCS modify other ‘behaviors’?

Did it feel the same?

What brain region helps respond to that question?

Beware of circular ‘experimental designs’
Brain Behavior Relations

Genetic Defect → Environmental Factors → Acquired Insult → Pathology

Brain Adaptation/Compensation → Change in Cognitive Strategy → Pathology

Pattern of Brain Activity

Behavior

Symptoms of Disease
Neurons or Networks?

$10^{12}$ Neurons

$10^4$ Connections per neuron

$10^{18}$ Synapses
Modulating Brain’s Intrinsic Activity with tDCS

A

DAY 1

tDCs Sham 20min  \rightarrow  R-fMRI 10min  \rightarrow  tDCs Real 20min  \rightarrow  R-fMRI 10min

\approx1\text{ month}

DAY 2

tDCs Sham 20min  \rightarrow  R-fMRI 10min  \rightarrow  tDCs Real 20min  \rightarrow  R-fMRI 10min

B

ACTIVE
Stim off
Stim on
20 min

SHAM
Stim off
Stim on
30 sec
20 min
Modulating Brain’s Intrinsic Activity with tDCS
Modulating Brain’s Intrinsic Activity with tDCS
Parkinson’s

Dystonia

Essential Tremor

Tourette’s

Huntington’s

Alzheimer’s

○ Excitatory stimulation target
○ Inhibitory stimulation target

Negative Correlation  Positive Correlation
Targeting brain patterns (& oscillations) with tDCS / tACS

Rs-fcMRI with Subgenual

Simulated E field

Collaboration with Giulio Ruffini and StarStim
What do we know?

- Safe if done correctly
- Easy to apply
- Double blinding possible
  - Subject cannot tell whether anodal or cathodal
  - Subject cannot tell whether sustained or transient stim

**DEPENDS ON DOSE !!**
Davis et al Eur J Neurosci. 2013
Why do tDCS?

- Modify brain activity during stimulation and beyond

- Affect behavior
  - Causal relations between brain activity and behavior
  - Prime brain activity to ‘enhance’ impact of behavioral intervention, task performance
When do tDCS?

- Before – During – After Task

Diagram:
- Before Offline
- During - Online
- After - Offline
For how long to do tDCS?

- Membrane effect
- Network impact with induction of plastic changes
- ? LTP- or LTD-like effects

How long does the effect last?
For how long to do tDCS?

- Interaction between tDCS and ongoing brain activity in the brain
  - Nature of the task may affect the nature of the effects of tDCS
  - Different tasks may modify tDCS effects differently
  - More/longer tDCS may not necessarily mean more of the same effect
- Physiologic measures in addition to behavioral measures desirable
Effects of tDCS during a task may not be the same as the effects of tDCS alone.

Behavior

**tDCS**

- Neurophysiology
  - EEG – NIRS - MRI

Behavior

**Sham tDCS Control tDCS**

- Neurophysiology
  - EEG – NIRS - MRI

Behavior

Quantify
Transcranial (Direct) Current Stimulation

Value of Modelling
- But remember limitations!

Value of Integrated Neurophysiologic Monitoring
Precise Monitoring of Behavior
Combine tDCS with Robotic Support

Medina J, Vidal J, Tormos JM, et al
*Institut Guttmann*

Edwards D.J., Krebs H.I., Volpe B.
*Mechanical Engineering, MIT*
*Burke Rehab Institute, Cornell Univ. NY*
For how long to do tDCS?

Task

When does the effect of tDCS start?

- ‘local effect’
- Network impact – transynaptic distant/distributed impact
For how long to do tDCS?

- Metaplastic Effects
How much tDCS?

• How do we calculate the DOSE?
• Does the “dose” (induced brain current) map 1:1 onto behavioral effects?

• Interaction between brain activity and applied stimulation
  • More stimulation does not necessarily mean more of the same neurophysiologic or behavioral impact
Invasive brain stimulation for the treatment of neuropathic pain

Jean-Paul Nguyen, Julien Nizard, Yves Keravel & Jean-Pascal Lefaucheux
A sham-controlled, phase II trial of transcranial direct current stimulation for the treatment of central pain in traumatic spinal cord injury

Felipe Fregni a,*,1, Paulo S. Boggio b, de,1, Moises C. Lima c, Merari J.L. Ferreira d, Tim Wagner a, Sergio P. Rigonatti c, Anita W. Castro e, Daniel R. Souza e, Marcelo Riberto e, Steven D. Freedman a, Michael A. Nitsche g, Alvaro Pascual-Leone a,f

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Using visual illusion to reduce at-level neuropathic pain in paraplegia

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Received 23 September 2006; revised in revised form 8 January 2007; accepted 11 January 2007

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**Diagram Description**

- **Image seen by patient in mirror**
  - Buttons and VAS
  - Legs out of sight
- **Screen**
  - **A**
    - Pain graph showing changes over time
  - **B**
    - Pre and Post images
      - Film
      - Imagery
      - Virtual walking

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**Text**

- Clinical note
- Using visual illusion to reduce at-level neuropathic pain in paraplegia
- G. Lorimer Moseley *
- Department of Physiology, Anatomy and Genetics and MSK Centre, University of Oxford, Neurone Clinic Building, South Parks Road, Oxford OX3 7LS, United Kingdom
- Received 23 September 2006; revised in revised form 8 January 2007; accepted 11 January 2007
Effective transcranial direct current stimulation and visual illusion on neuropathic pain in spinal cord injury

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1 Institut Guttmann. Hospital de Neurorehabilitació, Institut Universitari adscrit a la Universitat Autònoma de Barcelona, Barcelona, 08916 Badalona, Spain
2 Berenson-Allen Centre for Noninvasive Brain Stimulation, Department of Neurology, Beth Israel Deaconess Medical Centre and Harvard Medical School, 330 Brookline Avenue, KS-158 Boston, MA 02215, USA
3 Institut de Neurociencies, Universitat Autònoma de Barcelona and CIBERNED, 08193 Bellaterra, Spain
Soler et al, *Brain* 2010
Soler et al, *Brain* 2010
HOWEVER, tDCS ALONE HAS IMPACT ON DIFFERENT ASPECTS OF PAIN THAN tDCS COMBINED WITH VR
Charles LeRoy (1750’s)
Challenges of Visual Restoration
Challenges of Visual Restoration
Opportunities for Visual Restoration/Restitution

Sensory Substitution

Auditory Cortex

Somatosensory Cortex

Visual Cortex

Other Visual Areas

Visual Retraining

Promote Visual Plasticity
VRT

- 6 mo of Rx
- > 3 x/ per wk
- VF gain ± 4 deg
Can the effect of VRT be enhanced by tDCS?

3 Months
3x / wk

Training
- 30 min X twice a day
- 3 days/week
- Total of 3 months
Can the effect of VRT be enhanced by tDCCS?
Can the effect of VRT be enhanced by tDCS?

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age, y</th>
<th>Location of Lesion</th>
<th>Type of Lesion</th>
<th>Affected Side</th>
<th>Type of Visual Field Deficit</th>
<th>Postlesion Duration, mo</th>
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<td>VRT + tDCS</td>
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<tr>
<td>1</td>
<td>F</td>
<td>32</td>
<td>L occipital and medial temporal</td>
<td>Stroke</td>
<td>Right</td>
<td>Hemianopia</td>
<td>22</td>
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<td>2</td>
<td>M</td>
<td>70</td>
<td>L frontoparietooccipital</td>
<td>Stroke</td>
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<td>Quadrantanopia</td>
<td>21</td>
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<td>3</td>
<td>F</td>
<td>61</td>
<td>L occipital</td>
<td>Stroke</td>
<td>Right</td>
<td>Hemianopia</td>
<td>72</td>
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<td>4</td>
<td>M</td>
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<td>Hemorrhage</td>
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<td>Hemianopia</td>
<td>3</td>
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<td>6</td>
<td>M</td>
<td>47</td>
<td>R Parieto-occipital</td>
<td>Stroke</td>
<td>Left</td>
<td>Quadrantanopia</td>
<td>3</td>
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<tr>
<td>VRT + sham</td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>7</td>
<td>F</td>
<td>62</td>
<td>L occipital</td>
<td>Stroke</td>
<td>Right</td>
<td>Hemianopia</td>
<td>10</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>66</td>
<td>R occipital</td>
<td>Resection</td>
<td>Left</td>
<td>Hemianopia</td>
<td>192</td>
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<tr>
<td>9</td>
<td>M</td>
<td>69</td>
<td>L occipital and R frontoparietal</td>
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<td>Hemianopia</td>
<td>96</td>
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<tr>
<td>10</td>
<td>M</td>
<td>58</td>
<td>L medial occipital</td>
<td>Stroke</td>
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<td>Quadrantanopia</td>
<td>21</td>
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<td>11</td>
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<td>74</td>
<td>R temporoparietal and L frontal</td>
<td>Stroke</td>
<td>Left</td>
<td>Hemianopia</td>
<td>23</td>
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<tr>
<td>12</td>
<td>F</td>
<td>60</td>
<td>L occipital</td>
<td>Resection</td>
<td>Right</td>
<td>Quadrantanopia</td>
<td>10</td>
</tr>
</tbody>
</table>

Abbreviations: VRT, Vision Restoration Therapy; tDCS, transcranial direct current stimulation; L, left; R, right.
Can the effect of VRT be enhanced by tDCS?

Plow et al *Physical Med & Rehab* 2011; *Neurorehab Neural Repair* 2012
Anodal tDCS can enhance the effects of VRT

**Change in Visual Field**

<table>
<thead>
<tr>
<th></th>
<th>Pre-Int1</th>
<th>Pre-Int2</th>
<th>Pre-Post</th>
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<tbody>
<tr>
<td>VRT + Active tDCS</td>
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<td></td>
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</tr>
<tr>
<td>VRT + Sham tDCS</td>
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<td></td>
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</table>

Plow et al *Physical Med & Rehab* 2011
How does anodal tDCS enhance the effects of VRT?

How does anodal tDCS enhance the effects of VRT?

Brain Stimulation to Promote Visual Restoration/Restitution
Although the **number of publications** concerning the use of tCS in human brain studies has **exponentially increased** along last decade, little is known about basic mechanisms underlying tCS effects.

Nevertheless, **basic knowledge is urgently needed** in order to:

a) **establish safety limits** for electrical brain stimulation
b) **design new experimental protocols** aiming to optimize tCS effects
c) perform systematic studies of tCS effects on neuronal pathological states
d) **explore tCS potential uses** for computer-to-brain interaction.

Understanding of different tCS aspects requires from **direct electrophysiological measurements**, **fine pharmacological manipulation** of local networks and **precise histological and molecular characterization** → ¡¡¡animal models!!!
Transcranial direct-current stimulation modulates synaptic mechanisms involved in associative learning in behaving rabbits


aDivision of Neurosciences, Pablo de Olavide University, 41013 Seville, Spain; bInstitut National de la Santé et de la Recherche Médicale U642, Rennes F-35000, France; cLaboratoire Traitement du Signal et de L’Image, Université de Rennes 1, Rennes F-35000, France; dNeuroelectrics, 08022 Barcelona, Spain; and eStarlab Barcelona SL, 08022 Barcelona, Spain
Associative learning: classical conditioning

1. Before conditioning
   - Unconditioned stimulus: Food
   - Unconditioned response: Salivation

2. Before conditioning
   - Neutral stimulus: Whistle
   - No response

3. During conditioning
   - Whistle + Food
   - Unconditioned response: Salivation

4. After conditioning
   - Whistle
   - Conditioned stimulus: No salivation
   - Conditioned response: Salivation

Ivan Pavlov, 1903
Classical conditioning of the eyeblink reflex

Air puff

O.O. EMG

C1
C2
C3
C4
C5
C6
C7
C8
C9

Train

Air puff

O.O. EMG

C1
C2
C3
C4
C5
C6
C7
C8
C9

CS

US

1 mV

200 ms
tDCS effects over the somatosensory cortex of rabbits

Experimental design

Air puff duration: 100 ms
Frequency: $15 \pm 3$ s
3.7 A/m² (maximum value) for 1 mA

Current intensity distribution based on spherical model
tDCS effects over the somatosensory cortex of rabbits

Short-term effects

First direct evidence of tDCS effects on cortical excitability in the alert animal.

(Márquez-Ruiz et al., 2012, PNAS USA)
tDCS effects over the somatosensory cortex of rabbits

Long-term effects

Only cathodal tDCS effects over SS cortex induce significant poststimulus changes confirming experiments in human cortex.

Dieckhöfer et al., 2006, Clinical Neurophysiology

(Márquez-Ruiz et al., 2012, PNAS USA)
tDCS effects over the somatosensory cortex of rabbits

Long-term effects blockade

DPCPX: A1 adenosine receptor antagonist

A1 adenosine receptor is implied in the LTD-like process observed after cathodal stimulation.

(Márquez-Ruiz et al., 2012, PNAS USA)
tDCS effects over the somatosensory cortex of rabbits

Presynaptic effects

Márquez-Ruiz et al., 2012, *PNAS USA*
tDCS effects over the somatosensory cortex of rabbits

Presynaptic effects
tDCS effects over the somatosensory cortex of rabbits

Presynaptic effects

tDCS modifies thalamocortical synapses at presynaptic sites
tDCS effects on classical eyeblink conditioning

(Márquez-Ruiz et al., 2012, PNAS USA)
tDCS effects on classical eyeblink conditioning

(Márquez-Ruiz et al., 2012, *PNAS USA*)
tDCS effects on classical eyeblink conditioning

(Márquez-Ruiz et al., 2012, *PNAS USA*)

tDCS can modulate the acquisition of associative learning probably decreasing or increasing sensory perception process.
tDCS effects over the somatosensory cortex of rabbits
Histological analysis
tDCS effects over the somatosensory cortex of rabbits

Histological analysis