Transcranial Direct Current Stimulation (tDCS)

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Rationale of Electrotherapy

- Broad spectrum (neuropsychiatric, rehabilitation, cognitive performance…)
- Individualized therapy
- Targeted brain modulation (space + time)
- Adverse effects (minimal complications + counterindications)
- Mechanisms of action vs. mechanisms of disease
- Cost

Is DC stimulation an advantageous technique in this scenario?
What are the options?

Different electrodes/coils

A) Transcranial Electrical
B) Transcranial Magnetic
C) Invasive Leads
(Also Vagus, Spinal..)

Figure from Marom Bikson
Brain Electrotherapy

Figure from Marom Bikson
What is tDCS?

- Very simple, safe and powerful technique of **neuromodulation** *(not neurostimulation)*

- *Should we call Transcranial neuromodulation with DC?*

- Based on a constant electric field

- Used for more than 200 years - Galvanization (Based on the experiments of Aldini - beginning of XIX century - Italy - nephew of Galvani)*
Why DC stimulation?

- Modulates spontaneous neuronal activity
- No disruptive effects (compared to TMS and DBS)
- Non-expensive
- Reliable sham condition
- Easy to administer (clinical applications)
- Less adverse effects
Basic principle of brain polarization

Charged particles/proteins/ions move along the gradient of voltage.
How does this affect neuronal activity?

- Changes in PH
- Changes in Membrane Protein
- Changes in ions
- Glial changes
Direct effects of DC stimulation

Goldring, 1950
How does transcranial DC stimulation work in humans?
But...Does the current reach the cortex?

- Computer modeling studies
- Neurophysiological data
- Behavioral data
Several studies have been performed (animal and human models)

They showed that a significant amount of current reaches cortical surface - enough to induce biological effects if the duration of stimulation is appropriate.
tDCS model 1

Wagner et al, - Neuroimage, 2007
tDCS model 2
tDCS model 3

“Conventional” transcranial electrotherapy

Bikson et al, Brain Stimulation, 2009
Neurophysiological data

- Animal studies (experiments conducted in the 50s, 60s and 70s) - direct neuronal recording
- Human studies (cortical excitability studies - use of single pulse TMS, EEG and neuroimaging)
Intracellular activities and evoked potential changes during polarization of motor cortex –

Purpura and McMurtry, 1964
Initial studies with tDCS/TMS-MEP

Study by Priori et al. - 1998

- Short conditioning anodal DC pulses leads to MEP depression – cathodal induces no effects

- Differences – electrode montage (extracephalic – chin) - intensity
After-effects of anodal transcranial direct current stimulation (tDCS) on motor cortical excitability

Additional evidence

- Neuroimaging studies (PET, fMRI, MRS)
- EEG studies
- Additional animal studies

Lang, European Journal of Neuroscience, 2005
Synaptic vs. non-synaptic effect
Non-synaptic effects
Intracellular activities and evoked potential changes during polarization of motor cortex –

Purpura and McMurtry, 1964
Membrane effect?

Effect of cathodal transcranial direct current stimulation (tDCS) on resting motor threshold (A) and on motor evoked potentials (MEP amplitude) (B,C) elicited by transcranial magnetic stimulation (TMS).

Effect of cathodal transcutaneous direct current (DC) stimulation and sham stimulation on the excitability of ulnar motor axons.

Ardolino et al., J Physiol, 2005
Cortical Spreading Depression

- Massive changes in ionic concentrations

- Slow nonlinear chemical waves - speeds on the order of mm/min

- Cortical effect

- Clearly involved with non-synaptic mechanisms
Cortical Spreading Depression

Liebetanz, Neuroscience Letters, 2006
Synaptic effects
Evidence for synaptic effects
Pharmacological studies – intra-effects

CBZ - carbamazepine
DMO - N-methyl-D-aspartate (NMDA)-receptor antagonist dextromethorphan
FLU - (calcium channel blocker) - flunarizine

Drug-induced modulation of tDCS-driven cortical excitability changes during stimulation

Nitsche, J Physiology, 2003
Pharmacological effects - after-effects

CBZ - carbamazepine
DMO - N-methyl-D-aspartate (NMDA)-receptor antagonist dextromethorphan

TMS-elicited MEP amplitudes before and after 5 min of anodal and cathodal tDCS, under different pharmacological conditions

Comparison of post-stimulation MEP amplitudes after intake of CBZ or placebo

Evidence of LTP

- Experiment with mice
- In vitro direct current stimulation
- Demonstrate anodal stimulation results in long term synaptic plasticity (DCS-LTP)
  - polarity specific
  - NMDA receptor dependent
  - requires coupling of DCS with repetitive low-frequency synaptic activation (LFS)

(Fritsch et al., 2010)
Preliminary Study

- Study led by Alexander Rotenberg (CHB)
- Top panel: enhanced CA1 EPSP following DC stimulation of hippocampal slice.
- Bottom panel: increased CA1 EPSP slope following DCS of hippocampal slice (blue line indicates stimulation for 30 min – 75uA).
Where can tDCS be explored?

- tDCS might be an optimal tool to modulate *practice-related learning neural activation*

- Changes in network associated with practice

- Enhancement might be useful for initial stages of learning during skills acquisition and at later stages for learning of new skills

- Can tDCS guide and be used to guide these effects?
Other Issues
Safety of extracephalic reference electrodes in humans

- Study by Vandermeen et al., 2010
  - Testing safety of extracephalic electrodes in tDCS on healthy human volunteers.
  - Seeing effects on autonomic functions of brain stem (including respiration, heart rate etc.)
  - No significant effects between anodal, cathodal or sham stimulation for BP and HR for subjects

Conclusions from study: stimulation did not significantly modulate brain stem activity, and therefore may be safe to use in healthy volunteers using same parameters, though this study is limited.

Vandermeeren et al. BMC Neuroscience 2010 11:38
Extracephalic electrodes

Clinical and modeling study (study led by Mariana Mendonça)

Effects of unipolar stimulation in fibromyalgia

Initial studies have shown that M1 stimulation is associated with significant analgesic effects

tDCS montage – M1-SO

Unexpected behavioral results
Optimal stimulation protocols – duration of effects

- Can tDCS after-effects be prolonged?

- Repetitive stimulation is already performed in clinical applications.

- Cathodal tDCS-induced cortical excitability alterations with different protocols (9-min duration; 1 mA) with an interstimulation interval of 0 (no break), 3, or 20 min or 3 or 24 h were performed.
Safety

- Animal study – Liebetanz et al, 2009
- 58 rats - cathodal stimulations at 1–1000 mA for up to 270 min through an epicranial electrode (3.5 mm²).
Safety issues

- Systematic review of adverse effects
- Aiming to assess tDCS safety in different conditions and study designs
- Systematic review and meta-analysis of tDCS clinical trials.
- Articles from 1998 (first trial with contemporary tDCS parameters) to August 2009.
KEYWORDS
“Transcranial direct current stimulation” OR “tDCS” or “brain polarization” OR “galvanic stimulation” FROM 1998 TO AUGUST 2009

263 articles retrieved

132 articles excluded:
- Animal studies
- Review articles
- Duplicate data
- Other stimulation techniques

131 articles (157 studies) included

87 studies assessed Adverse Events

47 studies reported at least one Adverse Event

Six studies quantified Adverse Effects
In the subsample reporting AEs:

Most common were, for active vs. sham group:

- itching (35.6% vs. 25%, p<0.01)
- tingling (17.2% vs. 9.6%, p<0.01)
- headache (10.3% vs. 13.5%, p=ns)
- Burning sensation (5.8% vs. 7.7%, p=ns)
- Discomfort (1.2% vs. 1.92%, p=ns).

More severe adverse effects: skin burns and sensation of shock (local conditions are important to be assessed)

Local pain should not be considered as the only predictor for lesion
Study | OR (95% CI) | Weight
---|---|---
Fregni (2006) | 0.22 (0.02, 2.04) | 16.87
Boggio (2008) | 0.31 (0.01, 8.30) | 10.80
Fregni (2006) | 1.47 (0.05, 39.12) | 10.84
Boggio (2007) | 1.22 (0.21, 7.11) | 20.32
Fregni (2008) | 2.33 (0.38, 14.26) | 19.96
Fregni (2008) | 15.40 (2.93, 80.95) | 21.20
Overall (I-squared = 55.3%, p = 0.048) | 1.57 (0.41, 5.95) | 100.00

NOTE: Weights are from random effects analysis
Alternatives – Ring Electrodes
Marom Bikson
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High-density transcranial electrotherapy hardware