Methodological considerations for tDCS

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A technical guide to tDCS, and related non-invasive brain stimulation tools

Motivation

- tDCS is increasingly applied
- Seemingly simple tool
- Inappropriate use can lead to frustrating results
- Not all practically relevant information readily available
Overview

• Devices and application

• Protocols

• Physiological effects

• Functional effects in healthy humans and patients
Devices I
Devices II

✓ Numerous CE-certified devices available

✓ Different characteristics (MRI-suited, multiple channel, wireless, simultaneous EEG, home-use units, range of stimulation modes)

✓ Test for appropriate current flow!
Electrodes - Types
Electrodes – Contact Medium

- Saline and cream are suitable
- Saline: not too wet and not too dry...
- Cream: sufficiently thick film
- Electrode shape and distance are relevant

Miranda et al. 2009, Palm et al. 2014
Electrodes – Placement I

Electrode position: ccoem, cc-ef, oo-ef, oo-pom, m-cm, of-pom

- Anodal stimulation
- Cathodal stimulation

Nitsche & Paulus 2000
Moliadze et al. 2010
Datta et al. 2012
Electrodes – Placement II

- Standard systems (e.g. 10 20 EEG)
- Neuronavigation (MRI-based)
- Physiology-based
Electrodes – Placement III

- Not too tight
- Not too loose
- Not too wet
- Not too dry
- Constant position
- Not too close
Conclusions - Devices

• Different devices for different needs available
• Make sure that stimulators deliver current as expected!
• Electrodes come in different shapes and designs
• Saline solution and cream/gel suited
• Take care for constant and correct positioning!
Stimulation protocols

- Stimulation duration and intensity
- Focality of stimulation
- Blinding
- Safety
Stimulation duration

4 seconds

5-13 min

Stimulation duration and intensity

13 vs 26 min anodal tDCS

1 vs 2 mA cathodal tDCS

Longer and stronger is not always better

Batsikadze et al. 2013, Monte-Silva et al. 2013
Transferability to other cortices?

Visual cortex

Somatosensory cortex

Antal et al. 2004, Matsunaga et al. 2004
Shaping effects of tDCS by systematic protocol adaptation

Cuypers et al. 2013, Boggio et al. 2006
Conclusion Protocols I

- Protocols inducing acute and after-effects available
- Longer and stronger stimulation does not always increase efficacy
- Repetition can result in bidirectional interference effects
- Not identical effects in all areas
- Titration of effects preferable for new areas
Focalizing by reducing the size of the stimulation electrode
Focalizing by use of an extracephalic return electrode?
Focalizing by modification of electrode shape?

Kuo et al., 2013
Enhanced focality (?)

Fig. 1. Montages used during stimulation, derived from HDExplore™ and HDTargets™ software: A, anodal stimulation to the LDLFPC (anode: F3; cathodes: AF3, F6, FC, FC3). B, Anodal stimulation to the PT (anode: C6; cathodes: CS, TP7, C3, P6). C, Electrode configuration resulting in anodal stimulation of the LMTL (anode: P9; cathodes: Fp1, Fp2, FC4). D, Sham montage (anode: F4; cathodes: C4, C6). E, Model simulation using HDExplore™ of the pattern of current strength associated with the LMTL montage designed to maximally stimulate the left hippocampus.

Fig. 3. Verbal learning scores, as calculated by the difference between final and initial blocks of the Rey's Auditory Verbal Learning Test (RAVLT), for each stimulation condition. *p < .05.

Nikolin et al., 2015
New multi-electrode approach

„monopolar“

„bipolar“

Ruffini et al. 2015
Increasing the efficacy of tDCS by network stimulation

Fischer et al., 2017
Conclusion Protocols II

- Focality of tDCS can be increased
- ...by altering electrode size
- ...by altering electrode configuration
- ...by altering electrode position
- Application-dependent usefulness
- Physiological alterations induced by these alternative protocols not sufficiently explored so far in each case
Blinding of stimulation

- Ramping of stimulation
- Reliable blinding at 1 mA
- Might be not reliable for stronger stimulation
- Might be not reliable for repetitive sessions
- Reduction of tingling sensation by local anesthetics
- Active control

- Specific stimulators with coded stimulation
- One experimenter only conducts stimulation
- Reduction of stimulation-generated erythema with ketoprofen
Safety vs tolerability

Safety: induction of structural or functional *damage*

Tolerability: unintended or uncomfortable effects without damage
Safety and tolerability of tDCS I

- No NSE enhancement
- No brain edema
- No structural damage

### Adverse effects of tDCS during stimulation in different groups of participants

<table>
<thead>
<tr>
<th>Participants</th>
<th>Tingling</th>
<th>Itching sensation</th>
<th>Burning sensation</th>
<th>Pain</th>
<th>Headache</th>
<th>Fatigue</th>
<th>Difficulties in concentrating</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>Mean intensity</td>
<td>N (%)</td>
<td>Mean intensity</td>
<td>N (%)</td>
<td>Mean intensity</td>
<td>N (%)</td>
</tr>
<tr>
<td>Migraine patients</td>
<td>6 66.7</td>
<td>1.67 ± 0.82</td>
<td>2 22.2</td>
<td>2.0 ± 1.41</td>
<td>1 11.1</td>
<td>2.0 ± 0</td>
<td>1 11.1</td>
</tr>
<tr>
<td>Post-stroke patients</td>
<td>2 33.3</td>
<td>1.9 ± 0</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
</tr>
<tr>
<td>Tinnitus sufferers</td>
<td>8 80</td>
<td>1.13 ± 0.35</td>
<td>3 30</td>
<td>1.0 ± 0</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
</tr>
<tr>
<td>Patients total</td>
<td>16 64</td>
<td>1.31 ± 0.60</td>
<td>5 20</td>
<td>1.4 ± 0.89</td>
<td>2 8</td>
<td>1.5 ± 0.70</td>
<td>9 36</td>
</tr>
<tr>
<td>Healthy subjects</td>
<td>56 72.7</td>
<td>1.86 ± 0.86</td>
<td>17 22.7</td>
<td>1.65 ± 0.93</td>
<td>14 18.2</td>
<td>1.4 ± 0.74</td>
<td>27 35.1</td>
</tr>
<tr>
<td>Participants total</td>
<td>72 70.6</td>
<td>1.74 ± 0.84</td>
<td>31 30.4</td>
<td>1.6 ± 0.72</td>
<td>22 16.6</td>
<td>1.59 ± 0.91</td>
<td>16 15.7</td>
</tr>
</tbody>
</table>

| Participants       | N (%)    | Mean intensity    | N (%)             | Mean intensity | N (%)    | Mean intensity | N (%) | Mean intensity | N (%) | Mean intensity | N (%) | Mean intensity |
|--------------------|----------|-------------------|-------------------|------|----------|---------|----------------------------|
|                    | N (%)    | Mean intensity    | N (%)             | Mean intensity | N (%)    | Mean intensity | N (%) | Mean intensity | N (%) | Mean intensity | N (%) | Mean intensity |
| Migraine patients  | 1 11.1   | 1.0 ± 0           | 2 22.2            | 1.0 ± 0       | 3 33.3   | 4 44.4         | 0     | 0               |
| Post-stroke patients| 0 0      | 0 0               | 1 16.7            | 1.0 ± 0       | 1 16.7   | 1 16.7         | 0     | 0               |
| Tinnitus sufferers | 0 0      | 0 0               | 0 0               | 1.0 ± 0       | 0 0      | 1 10           | 1     | Drowsiness      | –      | –               |
| Patients total     | 1 4      | 1.0 ± 0           | 3 12              | 1.0 ± 0       | 4 16     | 6 24           | 1     | Drowsiness      | –      | Nausea          |
| Healthy subjects   | 4 5.2    | 1.0 ± 0           | 15 19.5           | 1.29 ± 0.47   | 7 9.1    | 11 14.3        | 1     | Drowsiness      | 1 10   | 1.0 ± 0         |
| Participants total | 5 4.9    | 1.0 ± 0           | 18 17.7           | 1.24 ± 0.44   | 11 10.8  | 17 16.7        | 2     | Drowsiness      | 1 10   | 1.0 ± 0         |

Safety and tolerability of tDCS II

This review updates and consolidates evidence on the safety of transcranial Direct Current Stimulation (tDCS). Safety is here operationally defined by, and limited to, the absence of evidence for a Serious Adverse Effect, the criteria for which are rigorously defined. This review adopts an evidence-based approach, based on an aggregation of experience from human trials, taking care not to confuse speculation on potential hazards or lack of data to refute such speculation with evidence for risk. Safety data from animal tests for tissue damage are reviewed with systematic consideration of translation to humans. Arbitrary safety considerations are avoided. Computational models are used to relate dose to brain exposure in humans and animals. We review relevant dose–response curves and dose metrics (e.g. current, duration, current density, charge, charge density) for meaningful safety standards. Special consideration is given to theoretically vulnerable populations including children and the elderly, subjects with mood disorders, epilepsy, stroke, implants, and home users. Evidence from relevant animal models indicates that brain injury by Direct Current Stimulation (DCS) occurs at predicted brain current densities (6.3–13 A/m²) that are over an order of magnitude above those produced by conventional tDCS. To date, the use of conventional tDCS protocols in human trials (≤40 min, ≤4 milliamperes, ≤7.2 Coulombs) has not produced any reports of a Serious Adverse Effect or irreversible injury across over 33,200 sessions and 1000 subjects with repeated sessions. This includes a wide variety of subjects, including persons from potentially vulnerable populations.
Conclusion - Safety and tolerability of tDCS

• Well tolerated, no serious adverse effects
• Applies to conventional protocols
• Side effects can be monitored by tDCS questionnaires (e.g. Poreisz et al. 2007)
• Side effects like skin burns reported caused by inappropriate application
Monitoring physiological effects of tDCS - preconditions

- Participants in relaxed, stable state
- Test session might help
- Avoid unintended interference effects in case of multiple sessions
- Avoid interference effects between stimulation and monitoring method
Monitoring physiological effects of tDCS - methods

- Cortical excitability
- Motor evoked potentials
- Visual phosphenes
- TMS-EEG
- Cortical activity
- Resting EEG
- EP
- ERP
- Cortical activity
- Functional MRI
- BOLD
- ASL
- MRS
- Structural MRI
Monitoring physiological effects of tDCS - TMS

- Reliable hot spot and coil position
- Reliable baseline
- Constant state throughout experiment
- Sufficient number of stimuli (20 or more)
- No muscle activity before TMS
- TMS EEG over regions which do not induce relevant muscle contraction
Monitoring physiological effects of tDSCS - EEG

- Online or offline
- Online: cave artifacts, no EEG electrodes under stimulation electrodes
- Offline: cave conductivity alterations at former tDSCS electrode positions
- Solution: integrated approaches with recording/stimulation electrodes

Polania et al. 2011, Antal et al. 2004
Monitoring physiological effects of tDCS - MRI

• Online or offline

• Online: cave artifacts, MRI-suited tDCS system required

• Offline: tDCS outside scanner will cause delay, and enhance „noise“ due to altered head position

• No saline-moistened sponges (will get dry)

• Mark electrode positions with oil capsules

• Cables parallel to magnet bore

• Sufficient sample size

Polania et al. 2011, Jamil et al. submitted
Conclusion - Monitoring physiological effects of tDCS

- Couple of methods are available
- Different temporal and spatial sensitivity
- Different restrictions with regard to areas
- Specific considerations to be followed to receive reliable results
Functional effects in healthy humans - Rationale

stimuli
• visual
• auditory
• somatosensory
• gustatory
• olfactory
• vegetative

 perception

behaviour
motor activity

cognition, motivation, emotion

Functional effects in healthy humans – relevant factors

- Timing of stimulation
- Stimulated area
- Type of task
- Bottom vs ceiling effects
Timing and area of stimulation

Serial reaction time task (SRTT)

Kuo et al. 2008, Nitsche et al. 2003, 2010
Task characteristics I

Effect of tDCS on motor learning
LM-RO

Effect of tDCS on motor learning
Left VS-Cz

non  anodal  cathodal

Antal et al. 2004a,b
Task-characteristics II

The effect of tDCS on tracking movements

<table>
<thead>
<tr>
<th>Time</th>
<th>Cathodal</th>
<th>Anodal</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 min</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

V5-Cz
Oz-Cz
LM1-Fp3

The effect of tDCS on motion perception threshold

<table>
<thead>
<tr>
<th>Time</th>
<th>Cathodal</th>
<th>Anodal</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 min</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Non-e
Anodal
cathodal

Antal et al. 2004a,b
Ceiling effect – level of expertise

Furuya et al., in 2014
Functional effects in healthy humans

- Timing and area of stimulation should be adjusted to task-related physiology
- Task specifics affect stimulation impact
- Task should not be prone to bottom or ceiling effects
- Relatively fragile neuromodulatory effects; enhancing efficacy by repetition, and titration?
Functional effects in patients

Common rationale: Restitution of disturbed activity/excitability

Bihemispheric tDCS enhances language recovery but does not alter BDNF levels in chronic aphasic patients

Impact of transcranial direct current stimulation on fatigue in multiple sclerosis
Maximizing effects - titration

**PD - Intensity**

![Graph showing PD intensity changes over time.]

**Tinnitus - duration**

![Graph showing tinnitus duration changes over time.]

Batsikadze et al. 2013, Boggio et al. 2006

Shekhawat et al. 2013
Maximizing effects - repetition

**Stroke**

**Fibromyalgia**

Once daily repetition

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Boggio et al. 2007, Fregni et al. 2006
Maximizing effects – combination

**Table 1. Montgomery-Asberg Depression Rating Scale Scores at Different Times**

<table>
<thead>
<tr>
<th>Group of Factor</th>
<th>Baseline</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>% (SD)a</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Sham tDCS and placebo</td>
<td>30.76 (5.31)</td>
<td>21.37 (10.96)</td>
<td>-30.2 (30.7)</td>
<td>22.56 (5.50)</td>
</tr>
<tr>
<td>Active tDCS and placebo</td>
<td>30.76 (5.78)</td>
<td>20.53 (9.59)</td>
<td>-34.0 (26.8)</td>
<td>19.33 (10.41)</td>
</tr>
<tr>
<td>Active tDCS and sertraline</td>
<td>30.73 (5.72)</td>
<td>15.53 (7.90)</td>
<td>-46.5 (23.5)</td>
<td>15.70 (7.96)</td>
</tr>
<tr>
<td>P valuea</td>
<td>.99</td>
<td>.01</td>
<td>.9</td>
<td>.91</td>
</tr>
</tbody>
</table>

**Notes:**
- a: Paired t-tests were used to compare the baseline and post-treatment scores within each group.
- Group comparisons were performed using one-way ANOVAs followed by post-hoc comparisons using Tukey’s HSD test.

**Figure A:**
- Drug/stimulation condition
  - PLC, anodal
  - PLC, cathodal
  - CIT, anodal
  - CIT, cathodal

**Figure B:**
- MEP amplitude vs baseline
- Time course

Nitsche et al. 2009
Brunoni et al. 2012
Functional effects in patients - specifics

• Parameters such as stimulation intensity, duration, repetition and combination can be adjusted to optimize effects.
• The brain state of patients differ, and should be taken into account.
Concluding remarks

- Although seemingly simple to apply, tDCS studies require careful planning and conduction.
- Technical aspects of the intervention are often not taken sufficiently in account.
- Design aspects are critical for successful conduction.
- As neuromodulatory interventions, plasticity-inducing NIBS might be especially vulnerable to protocol problems.
- Most of the aspects discussed here are not specific to tDCS, but apply also to other NIBS protocols, and neuromodulatory interventions.