An Update on Blinding Practices in tDCS and tACS Research

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Importance of Blinding in Research

**Benjamin Franklin**

Blindfolded participants during “mesmerism”/sixth sense experiments

Performance worse when blindfolded

Revealed bias and importance of blinding

**Claude Bernard**

Wrote first seminal essays about blinding participants in order to promote objectivity
Importance of Blinding in Research

Benjamin Franklin

Blindfolded participants during experiments

Performance worse when blindfolded

Revealed bias and importance of blinding

Clever Hans

Smartest horse in the world?

or

“Reading” the investigator? (tension, facial expression, other unintentional cues)
Recommendations for Blinding in Research
A technical guide to tDCS, and related non-invasive brain stimulation tools

A.J. Woods a,*, A. Antal b, M. Bikson c, P.S. Boggio d, A.R. Brunoni e, P. Celnik f, L.G. Cohen g, F. Fregni h, C.S. Herrmann i, E.S. Kappenman j, H. Knotkova k, D. Liebetanz b, C. Miniussi l, P.C. Miranda m, W. Paulus b, A. Priori n, D. Reato c, C. Stagg o,p, N. Wenderoth q, M.A. Nitsche b,r,s
Recommendations for Blinding in Research

~ behavioral task - online, offline, both

~ voltage - <1 to 2.5 mA (most common 2, 1, 1.5)

~ duration – 1 to 60 min (most common 20, 15, 10)

~ montage – highly variable, study-specific
Did the study use a sham/placebo condition?
Blinding in tDCS Research - 2016

- Initial brief (+/- ramp) sham: 7%
- Initial brief (+/- ramp) sham - low V: 4%
- Initial and final brief (+/- ramp) sham: 7%
- Not defined: 1%
- Full active - opposite polarity: 84%
- Full active - off-target: 7%
- Full active (+/- ramp) - low V: 4%
- Partial active - low V: 4%
- Intermittent + ramp: 4%

N=173
Blinding in tDCS Research - 2016

Did the study assess effectiveness of sham condition?

N=173

25% YES

75% NO

How?

- sensation/AE questionnaire
- interview/briefing
- 3-choice questionnaire (+/- confidence rating)
- method not specified
Blinding in tDCS Research - 2016

Did the study report administrator blinding?

- Yes: 61%
- No: 39%

N = 173
Did the study assess administrator blinding?

98.8% of the studies (N=173) did not assess administrator blinding.

1.2% of the studies did assess administrator blinding.
Blinding in tDCS Research - 2016

Did the study report assessor blinding?*

92% (NO)
8% (YES)

N=204*
Did the study report rater blinding?

N=204*

96.6%

3.4%
Did the study collect and report sensation/AE data?

N=206

33%

67%

YES

NO
Blinding in tACS

- initial brief (+/- ramp) sham
- initial brief (+/- ramp) sham - low V
- initial and final brief (+/- ramp) sham - low V
- not defined
- full active - opposite
- full active - off-target
- full active (+/- ramp) - low V
- partial active - low V
- intermittent + ramp
- no sham

Different frequency (e.g., alpha)
<table>
<thead>
<tr>
<th>Blinding</th>
<th>Absent/Minimal Consideration or Reporting</th>
<th>Moderate Consideration or Reporting</th>
<th>Extensive Consideration or Reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Rationale for sham condition provided.</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2. Participant characteristics relevant to sham effectiveness reported (e.g., naïve v. experienced, old v. young, etc.).</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>3a. Participant blinding described.</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>3b. Participant blinding/unblinding monitored.</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>4a. Administrator blinding described.</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>4b. Administrator blinding/unblinding monitored.</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>5a. Assessor blinding described.</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>5b. Assessor blinding/unblinding monitored.</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>6a. Rater blinding described.</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>6b. Rater blinding/unblinding monitored.</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>7. Report when/for whom unblinding occurred, and why.</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Adapted from Richardson et al., in press and Gearing et al., 2011
Optimizing Rehabilitation for Phantom Limb Pain Using Mirror Therapy and Transcranial Direct Current Stimulation: A Randomized, Double-Blind Clinical Trial Study Protocol

STUDY PROTOCOL

Stroke Treatment Associated with Rehabilitation Therapy and Transcranial DC Stimulation (START-tDCS): a study protocol for a randomized controlled trial

Suellen M. Andrade, Natanael A. Santos, Bernardino Fernández-Calvo, Paulo S. Boggio, Eliane A. Oliveira, José J. Ferreira, Amanda Sobreira, Felipe Morgan, Germana Medeiros, Gyovanna S. Cavalcanti, Ingrid D. Gadelha, Jader Duarte, Joercia Marrocos, Michele A. Silva, Thatiana Rufino, and Sanmy R. Nobrega
Appendix A. (revised questionnaire, English version)

Subject code: ___________________________ Date: __/__/_____
Experiment: _____________________________

Did you experience any discomfort or annoyance during the electrical stimulation? Please answer the following questions regarding the different sensations and indicate the degree of intensity of your discomfort according to the following scale:

- None = I did not feel the described sensation (0)
- Mild = I mildly felt the described sensation (1)
- Moderate = I felt the described sensation (2)
- Considerable = I felt the described sensation to a considerable degree (3)
- Strong = I strongly felt the described sensation (4)

**In the first stimulation block**

- Itching:
  - None
  - Mild
  - Moderate
  - Considerable
  - Strong

- Pain:
  - None
  - Mild
  - Moderate
  - Considerable
  - Strong

- Burning:
  - None
  - Mild
  - Moderate
  - Considerable
  - Strong

- Warmth/Heat:
  - None
  - Mild
  - Moderate
  - Considerable
  - Strong

- Pinching:
  - None
  - Mild
  - Moderate
  - Considerable
  - Strong

- Metallic/Iron taste:
  - None
  - Mild
  - Moderate
  - Considerable
  - Strong

- Fatigue:
  - None
  - Mild
  - Moderate
  - Considerable
  - Strong

- Other ____________

When did the discomfort begin?
- At approximately the middle of the block
- Towards the end of the block

How long did it last?
- It stopped in the middle of the block
- It stopped at the end of the block

How much did these sensations affect your performance?
- Not at all
- Slightly
- Considerably
- Much
- Very much

Identify whether these sensations were located over the head or in a different location
- On the head __________
- Other __________

**In the second stimulation block**

...(If there is more than one condition, repeat the list above here based on the block numbers)

If you would like to provide more details, please briefly describe the experienced sensations in relation to the ‘Other’ or “Fatigue” response:

**To be administered at the end of the entire experiment**

Do you believe that you received a real or placebo stimulation?
- In the first stimulation block/day/week: real
- In the second stimulation block/day/week: real
- I don’t know

... 

For the researcher/clinician:

Please report any adverse event/problem (e.g., skin irritation, headache, scalp pain, dizziness, or others, please specify) that occurred and rate the event/problem on a scale from 1 to 4 as previously described.

Additional comments: ...
### Recommendation – Checklist/Questionnaire

**Appendix A. (revised questionnaire, English version)**

<table>
<thead>
<tr>
<th>Subject code: ___________________________</th>
<th>Date: <strong>/</strong>/_______</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experiment:</td>
<td></td>
</tr>
</tbody>
</table>

Did you experience any discomfort or annoyance during the electrical stimulation? Please answer the following questions regarding the different sensations and indicate the degree of intensity of your discomfort according to the following scale:

- **None** = I did not feel the described sensation (0)
- **Mild** = I mildly felt the described sensation (1)
- **Moderate** = I felt the described sensation (2)
- **Considerable** = I felt the described sensation to a considerable degree (3)
- **Strong** = I strongly felt the described sensation (4)

### In the first stimulation block

<table>
<thead>
<tr>
<th>Sensation</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Considerable</th>
<th>Strong</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itching</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burning</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Warmth/heat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pinching</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor tic/clonic twitching</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

When did the discomfort begin?
- [ ] At the beginning of the block
- [ ] At approximately the middle of the block
- [ ] Towards the end of the block

### In the second stimulation block

How long did it last?
- [ ] It stopped quite quickly
- [ ] It stopped in the middle of the block
- [ ] It stopped at the end of the block

How much did these sensations affect your performance?
- [ ] Slightly
- [ ] Considerably
- [ ] Much

Identify whether these sensations were located over the head or in a different location:
- [ ] On the head
- [ ] Other

#### Proposal of a questionnaire surveying for tDCS adverse effects

**tDCS Adverse Effects Questionnaire – Session**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Considerable</th>
<th>Strong</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neck pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Scalp pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tingling</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itching</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burning sensation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin redness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleepiness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Raco et al., 2014**

- [ ] Phosphenes
- [ ] Dizziness
- [ ] Pressure
- [ ] Skin sensations (other)

For the researcher/practitioner:
- Please report any adverse event/problem (e.g., skin irritation, headache, scalp pain, dizziness, or others, please specify) that occurred and rate the event/problem on a scale from 1 to 4 as previously described.

Additional comments: _____

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**Brunoni et al., 2011**

**Fertonani et al., 2011**
Recommendation – Questionnaire

5.1. Which treatment condition do you believe you received?

a) New treatment (active/full dose stimulation)
b) Placebo (sham stimulation)
c) Don’t know

5.2. If you answered ‘Don’t know’ above, can you please provide your best (or random) guess of a treatment you received anyway? (Please skip this question if you answered ‘a’ or ‘b’ above).

a). New/Active treatment
b). Placebo

5.3. On a scale of 0 to 10, how confident are you that you received (your selection)?

Adapted from Bang et al., 2010, Brinjikji et al., 2010, O’Connell et al., 2012, Zhang et al., 2013
7.1. Which treatment condition do you believe this participant received?

a) New treatment (active/full dose stimulation)

b) Placebo (sham stimulation)

c) Don’t know

7.2. If you answered ‘Don’t know’ above, can you please provide your best (or random) guess of a treatment the participant received anyway? (Please skip this question if you answered ‘a’ or ‘b’ above).

a). New/Active treatment

b). Placebo

7.3. On a scale of 0 to 10, how confident are you that the participant received (your selection)?
Recommendation – Devices, HD

Omochowski et al., 2013
Richardson et al., 2015

Garnett & den Ouden, 2015

Gbadeyan et al., 2016
Recommendation – Design and Analysis

- Recruitment/Participant Characteristics
- Consent
  - De Facto Masking?
    - participants, administrators, assessors
- Between groups instead of crossover
  - (does not free you from sham concerns)
- If crossover, analyze first-period data only
- Complementary active control and sham conditions
Recommendation – Sham Development

• A sham condition should be “indistinguishable”
  – equivalence testing instead of null-hypothesis testing?

• Sham development with investigators
  – If it works for a seasoned investigator, it should work for everyone
Thank You

Lab Members

Sarah Grace Dalton
Holly Stewart
Michaella Maddry

Departmental Collaborators

Rick Arenas

Mentors and Collaborators

Center for Brain Recovery and Repair

NIH